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°Livingston, S., and Petersen, D.: New England J. Med. **254**:327 (Feb. 16) 1956.

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INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

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1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.

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2. Schwab, R. S.: *Geriatrics 14*:545 (Sept.) 1959.
3. Doshay, L. J. *et al.*: *J.A.M.A. 160*:348 (Feb. 4) 1956.

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Neurology Volume 10 • Number 12

Motor nerve conduction in the carpal tunnel syndrome

P. K. Thomas, M.D., M.R.C.P.

CHANGES in motor nerve conduction in patients with lesions of the median nerve at the wrist were first reported by Simpson.[1] In a proportion of patients with the carpal tunnel syndrome, he showed that, when the median nerve was stimulated at the wrist and the evoked muscle action potential recorded from the abductor pollicis brevis or the opponens pollicis, the latency of the muscle response was increased. In this paper, the results obtained in 95 consecutive patients referred for routine electromyography with a clinical diagnosis of suspected compression of the median nerve in the carpal tunnel are described, together with observations on motor nerve conduction in the median nerve in a series of control subjects.

METHODS

The methods employed have been described in detail in an earlier paper[2] in which possible sources of error are discussed.

For stimulation of the median nerve, 3 standard cathode positions were adopted (Fig. 1). S1 was 2 to 3 cm. above the distal wrist crease. S2 was at the elbow, 2 to 3 cm. above the intercondylar line and just medial to the tendon of the biceps muscle. S3 was in the axilla. The stimulating cathode was a pad electrode 1 cm. in diameter and the anode (A in Fig. 1) a metal plate placed over the anterior aspect of the forearm or the lateral aspect of the upper arm. For the subjects examined at the National Hospital, the stimulus was a brief condenser discharge with a time constant of 150 μsec. At the Middlesex Hospital, a Stanco double-channel electromyograph was used, which provided a rectangular stimulating pulse of 100 μsec. duration. Stimuli were delivered through an isolating transformer, the stimulus intensity being always such that a

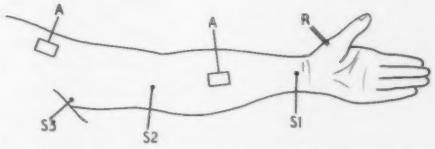

Fig. 1. Arrangement of stimulating and recording electrodes. For explanation, see text.

From the National Hospital, Queen Square, and the Middlesex Hospital, London.

further increase did not alter the size of the muscle response.

In all instances, recordings were made with a coaxial needle electrode (R in Fig. 1) placed in the abductor pollicis brevis. During stimulation, the position of the needle was carefully adjusted to ensure that the earliest response to the stimulus was obtained and that the initial deflection was as sharp as possible and the same for all 3 positions of the stimulating cathode. The potentials were amplified and displayed on 1 beam of a double-beam oscilloscope, the second beam of which carried a time scale.

The latency of the initial deflection of the muscle action potential was measured from photographic records and conduction time for the segments of nerve between the 3 cathode positions obtained by subtraction. Since the measurements were made to the initial deflection of the muscle potential, these values refer to the most rapidly conducting fibers.

The latency from the wrist to the muscle is a composite figure that includes the time taken for conduction in the most rapidly conducting nerve fibers to the muscle, the delay at the neuromuscular junction, and the time taken for conduction over the length of the muscle fibers between their innervation zone and the recording electrode. For this reason, no attempt was made to convert conduction time into velocity or make any other correction for conduction distance; the values obtained therefore include variations between individuals due to differences in size of the hand and the precise position of the electrodes. The distance between the wrist stimulating electrode and the recording needle in the muscle varied between 6 and 8 cm. in different subjects.

In the forearm and upper arm, a direct measurement of nerve conduction time is obtained and, in order to correct for differences in arm length, the results have been expressed as conduction velocity, employing surface measurements of interelectrode distance. The distance between the wrist and elbow stimulating positions varied from 25 to 30 cm. and, between the elbow and axillary positions, from 15 to 25 cm.

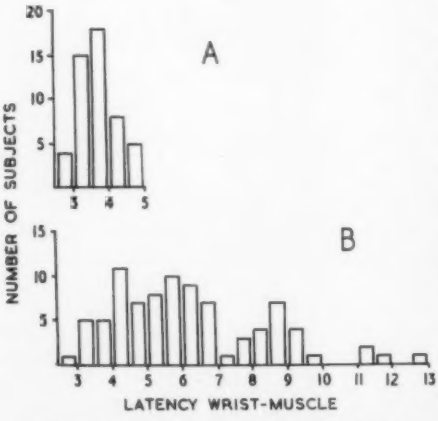

Fig. 2. [A] Distribution of latency of initial deflection of muscle action potential (in 0.5-msec. groups) in abductor pollicis brevis on stimulation of median nerve at wrist in 50 control subjects. [B] The same in 95 patients with suspected carpal tunnel syndrome; 2 patients with long latencies (19.5 and 26 msec.) are omitted. In a further 6 patients, median nerve was totally inexcitable.

RESULTS

Control subjects. In order to establish the normal range of variation, measurements of the latency of the initial deflection of the muscle action potential in the abductor pollicis brevis, on stimulation of the median nerve at the wrist, were made in 50 control subjects who were either healthy individuals or patients seen during routine electromyographic recordings because of an isolated lesion of another peripheral nerve. No difference between the 2 groups was apparent. The results are shown in Figure 2A; the individual values varied from 2.9 to 5 msec., the mean being 3.8 ± 0.5 msec. The age range was 19 to 65 years.

In 25 of the subjects, maximal conduction velocity over the forearm and upper arm was also measured, and the results are included in Figure 4. For the forearm, the mean value was 57.5 ± 5 meters per second with a range of 48.3 to 67.9 meters per second; for the upper arm, the mean was 59.8 ± 8.8 meters per second and the range 47.8 to 69.6 meters per second. Although conduction velocity was slightly greater in the upper arm, the difference is not statistically significant.

Conduction below wrist in patients with

suspected carpal tunnel syndrome. In all, 95 patients were examined—35 at the National Hospital and 60 at the Middlesex Hospital—in whom a diagnosis of the carpal tunnel syndrome was made or suspected by the referring physician. The latency of the initial deflection of the muscle action potential in the abductor pollicis brevis on stimulation of the median nerve at the wrist is shown for the whole group in Figure 2B. In 60, the value obtained exceeded the upper limit of normal. Latencies were at times grossly prolonged, the highest value recorded being 26 msec. In 6 patients, the muscle was found to be completely denervated, no motor unit potentials being recorded either on attempts at voluntary contraction or on electrical stimulation of the median nerve.

An illustrative record is shown in Figure 3. The patient (Mr. J.M.), a joiner aged 39, had a four-year history of an intermittent sensation of numbness involving the lateral 3 digits of the right hand and of nocturnal burning paresthesias in the same distribution, these symptoms gradually becoming increasingly troublesome. No abnormal findings were encountered on clinical examination, nor was any abnormality detected on routine electromyographic sampling of the right abductor pollicis brevis with a concentric needle electrode. However, on electrical stimulation of the median nerve at the wrist, the latency of the initial deflection of the muscle action potential was moderately increased, being 7.8 msec. The latencies on stimulation at the elbow and axilla were 12 and 14.6 msec., respectively, conduction velocity over the forearm being 50 meters per second and in the upper arm, 55.8 meters per second.

In considering individual cases, only those patients who show a latency that exceeds the upper limit of the normal range can be considered abnormal. However, it is clear from the histograms of Figure 2 that, for the patients in whom the latency is within the normal range, the distribution of the latencies is skewed in the direction of the higher values. This indicates that mild slowing of nerve conduction is also present in a proportion of these patients.

Conduction proximal to wrist in patients with carpal tunnel syndrome. In some of the

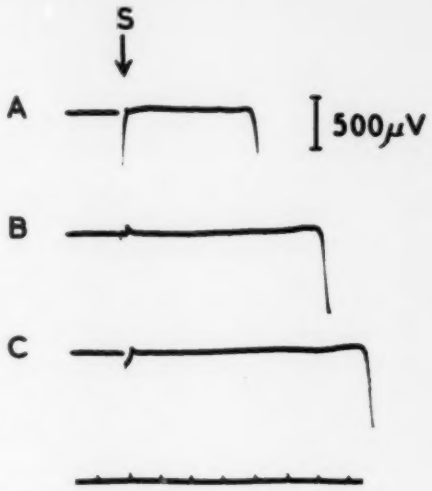

Fig. 3. Recordings from abductor pollicis brevis in a patient with carpal tunnel syndrome. For details, see text. Median nerve was stimulated at wrist (A), elbow (B), and axilla (C). Stimulus at S shown by artifact in each trace. Time scale: 2-msec. intervals

patients with the carpal tunnel syndrome, it was observed that motor nerve conduction time was not only increased distal to the wrist but that there was also a mild increase above the wrist, in both the forearm and upper arm. This was tested by estimating maximal conduction velocity over the forearm in 47 patients, all of whom showed a conduction delay distal to the wrist. The mean value for forearm conduction velocity in these patients was 49.3 $\pm$ 6.9 meters per second with a range of 36 to 65.9 meters per second. A similar estimation for the upper arm on 22 patients gave a figure of 50.2 $\pm$ 8.9 meters per second with a range of 34 to 63.2 meters per second. When compared with the values derived from the control series, these differences were found to be statistically significant ($P<0.001$ in both instances). Patients over the age of 65 were excluded from this analysis because conduction velocity is known to decrease in late life.

These results are illustrated in Figure 4, where conduction velocity over the forearm and upper arm for these patients has been

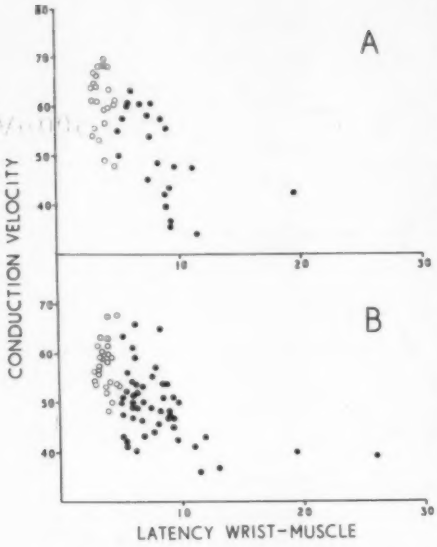

Fig. 4. Relationship between maximal motor nerve conduction velocity (in meters per second) over upper arm (A) and forearm (B) and latency of initial deflection of muscle action potential (in milliseconds) in abductor pollicis brevis on stimulation of median nerve at wrist in patients with carpal tunnel syndrome (filled circles) and in control series (open circles)

plotted against the latency of the muscle action potential in the abductor pollicis brevis on stimulation of the median nerve at the wrist and compared with the results of the control series. For the reasons stated earlier, the values for the wrist-muscle latency cannot be satisfactorily converted to conduction velocity. The open circles represent normal values and the filled circles the values for the patients. It is evident that the magnitude of the slowing of conduction velocity in the forearm and upper arm is related to the degree of slowing distal to the wrist; the greatest reduction in velocity, which is approximately 30% below the lower limit of the normal range, is found in patients with prolonged latencies in the hand.

DISCUSSION

The values for the latency of the muscle action potential in the abductor pollicis brevis on stimulation of the median nerve at the wrist in the control series agree well with those found by Simpson,[1] who also used needle electrodes for recording the muscle response. The values given by Carpendale[3] are slightly less but are not strictly comparable because surface recording electrodes were used. The figure of 57.5 meters per second obtained for mean conduction velocity over the forearm is similar to those of other series.[2,4,5] Redford[5] also estimated conduction velocity for the median nerve in the upper arm and likewise found no significant difference between the upper arm and forearm.

These values are somewhat low when compared with those usually obtained for other mammalian A fibers, but it is probable that the motor nerve fibers to the abductor pollicis brevis are relatively small. No fiber larger than 12 μ in diameter was found in the median nerve at the wrist by Ranson and associates.[6] A gradient of fiber size in the limb in mammals is known to exist such that the proximal limb muscles are innervated by larger fibers than the distal.[7] This is also likely to obtain in man, since Redford[5] found that conduction velocity for nerves to proximal limb muscles is greater than that for nerves to distal limb muscles, a finding confirmed in this laboratory.[8]

In the present series, slightly more than two-thirds of the patients showed a latency from the wrist to the abductor pollicis brevis that exceeded the upper limit of normal. This is the same proportion as was reported by Simpson,[1] who found an increased latency in 11 of 15 subjects with a clinical diagnosis of the carpal tunnel syndrome. Of the patients in the present study who showed latencies that were within the normal range, a few may represent misdiagnoses. However, as has already been mentioned, the distribution of the values lying within the normal range is skewed in the direction of the higher values, indicating an overlap between the pathologic and normal ranges. This reduces the sensitivity of the method as a diagnostic procedure, since, in the individual case, the criterion of abnormality is necessarily that the value should exceed the upper limit of normal. In the diagnosis of doubtful cases, the examination of the sensory nerve action potential obtained over the median nerve at the wrist on electrical stimulation

of the index finger[9] has proved to be a valuable additional test.

The cause of the slowing of conduction in the segment of median nerve distal to the wrist in the carpal tunnel syndrome is uncertain. Simpson[1] suggested that it was the result of ischemic changes in the compressed portion of nerve similar to those observed in acute human experiments by Kugelberg[10] and Kugelberg and Cobb.[11] However, this is unlikely to be the complete explanation in view of the profound degree of slowing in some of the cases and the long-time course of the recovery after surgical decompression of the nerve. For example, in some of the cases followed by Goodman and Gilliatt,[12] a progressive reduction in latency was observed over periods of up to eighteen months after operation. These observations suggest that structural changes in the nerve fibers are involved. An alternative explanation that has been considered is that the slowing represents conduction in regenerating fibers after wallerian degeneration. This is unlikely to account for the slight degrees of slowing in mild cases; it is impossible to imagine that, in these circumstances, all fibers could be at the same stage of regeneration and almost fully recovered.

A possible answer is to be found in the results of experimental constrictions applied to peripheral nerves. Weiss and Hiscoe[13] found that regenerating nerve fibers growing through a constricting zone showed a permanent deficit of diameter distal to the constriction. Similarly, Duncan[14] demonstrated that, when ligatures were applied to the nerves of young animals, growth in fiber diameter was impeded distal to the constriction. Neither of these experiments exactly parallels the situation in the carpal tunnel syndrome, which involves a prolonged and probably slowly developing compression of mature nerve fibers. However, Weiss and Hiscoe were also able to show, with constricting lesions applied to the nerves of adult animals, that some fibers persisted through the lesion without distal degeneration and still displayed a reduction in diameter distal to the constriction.

Although gross increases in latency were only seen in patients with clinical defects of motor function, it was not uncommon to encounter a mildly increased latency from the wrist to the abductor pollicis brevis in the absence of clinically detectable weakness or wasting of this muscle. It is of interest that Duncan[14] found in the rat that a considerable degree of constriction could be inflicted on a peripheral nerve, with consequent reduction in nerve fiber diameter distally, without evidence of functional loss or reduction in weight of the muscles supplied by the nerve.

The mild degree of slowing proximal to the wrist in patients with the carpal tunnel syndrome also requires comment. With regard to the forearm, it could be suggested that nerve compression at the wrist with or without the formation of a traumatic neuroma might produce changes for some distance above the flexor retinaculum in the same way that changes may extend for several centimeters above the lesion with a chronic traumatic ulnar neuritis at the elbow.[15] However, this could not explain the reduction of conduction velocity in the upper arm. A similar degree of slowing has been encountered proximal to lesions of the deep branch of the ulnar nerve in the hand[16] and after suture of the ulnar and median nerves at the wrist.[17] It is possible that this is equivalent to the slowing of conduction which has been demonstrated proximal to a variety of peripheral nerve lesions in the experimental animal[18–21] and which is associated with a reduction in fiber diameter. On the other hand, it is also possible that the lesion selectively damages the larger and more rapidly conducting fibers, as was shown for experimental constrictions by Weiss and Hiscoe.[13] Since the measurements of motor nerve conduction in the forearm and upper arm in the present study were made with the recording electrode distal to the lesion, the slowing may represent conduction in fibers of smaller caliber which have persisted through the compressed segment. It has been shown that the slowest extrafusal motor nerve fibers to the small muscles of the hand conduct at a rate 30 to 40% below the fastest,[2] and the degree of slowing proximal to the lesion in patients with the carpal tunnel syndrome is not greater than this.

SUMMARY

Observations on motor nerve conduction were made in 95 patients with a suspected

diagnosis of the carpal tunnel syndrome. With stimulation of the median nerve trunk just above the wrist, the latency of the muscle action potential in the abductor pollicis brevis was abnormally prolonged in approximately two-thirds. Conduction velocity was also moderately reduced over the forearm and upper arm in patients with a conduction delay distal to the wrist.

The significance of the electrical findings is discussed.

The author wishes to thank Dr. R. W. Gilliatt and Mr. T. A. Sears for helpful advice and criticism and Mr. H. B. Morton for technical assistance.

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Photoconvulsive and photomyoclonic responses in adults

An appraisal of their clinical significance

Kenneth A. Kooi, M.D., Madison H. Thomas, M.D., and F. Neal Mortenson, M.D.

THE USE of intermittent photic stimulation as an activating procedure in electroencephalography has led to the recognition of several types of cerebral and peripheral motor responses. We have previously studied photic "driving" in brain-damaged patients[1,2] and its variability in normal subjects.[3] The evoked cerebral patterns also include diffuse or anteriorly distributed spike and wave forms, spikey bursts, and delta and theta waves that are frequently polyrhythmic. The cerebral spike and wave response has been designated the "photoconvulsive" response by Bickford and associates[4] and the "fronto-central spike and wave" by Rémond[5] and Gastaut.[6] The oculofacial phenomenon has been variously described as the "photomyoclonic" response,[4] "photo-oculoclonic" reflex,[5] "fronto-polar," "recruiting," or "irradiated" response, and "frontal polyspikes."[7,8] In its usual form, it is to be distinguished from the "blink" or "opticofacial" reflex by its gradual progression during repetitive stimulation. In spite of the distinctive nature of these responses, their clinical implications have remained unsettled.

Studies by Walter and Walter, [9,10] Gastaut, Trevison, and Naquet,[6,11] Buchthal and Lennox,[12] Mundy-Castle,[13] Shagass,[14] Bonnet and Bonnet,[15] and Davidson and Watson[16] indicate that abnormal responses occur often but not exclusively in epileptic subjects. Bickford and associates[4] found that the photomyoclonic response occurred normally to high intensity light stimulation. Both Bickford[17] and Ulett[18] have described instances in which a seizure was induced in an individual without a history of epilepsy.

Although it seems clear that patients with seizures often have atypical responses to intermittent photic stimulation, the occurrence of similar responses and actual convulsions in control subjects throws considerable doubt upon their diagnostic specificity. However, differences in the criteria of abnormality, characteristics of the light source, and methods of presenting the photic stimulus in various laboratories make the results not strictly comparable. It would thus be desirable to establish a standard technic and test its efficacy in evoking photoconvulsive and photomyoclonic responses in both control and patient groups and, in addition, contrast clinical symptomatology in patients with and without such responses.

MATERIALS AND METHODS

Different technics of photic stimulation were utilized in the study of 2 patient and normal control series. A Grass Model PS-1 photic stimulator set at intermediate intensity was used throughout. In the technic used for the first series of 1,143 clinical examinations, the distance from the face of the flash lamp to the subjects' eyes was 15 cm. and twenty seconds of stimulation was carried out at 1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 20, 22, 24, 26, and 30 cps with twenty-second intervals between presentations. A period of stimulation in which the stimulus was varied between 3 and 20 cycles per second was also included. Also, 90 control subjects were examined with this technic. The second series of 1,105 clinical

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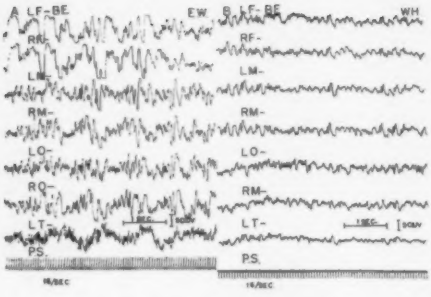

Fig. 1. Examples of photoconvulsive responses. [A] Diffuse spike and wave activity occurring only during photic stimulation. Effective frequencies—8, 10, 12, 16, and 20 cps. Movement artifacts in frontal and temporal derivations. [B] Spike and wave activity of less obvious character with central emphasis. Effective frequencies—12, 16, and 20 cps. In all figures, LF and RF = left and right frontal; LM and RM = left and right motor; LO and RO = left and right occipital; LT = left temporal; BE = both ears; P.S. = photic stimulation

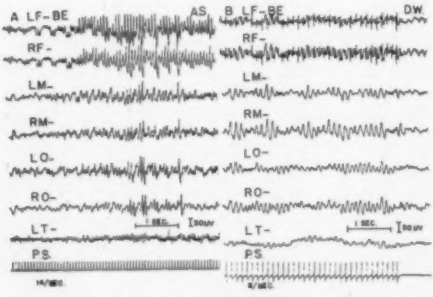

Fig. 2. Photomyoclonic responses. [A] Note initial recruitment with subsequent variability of muscle spike height. Response primarily in frontal area. Effective frequencies —12, 14, 16, and 20 cps. [B] Response recorded only in frontal area. Immediate cessation of response with last flash. Effective frequencies—8 and 10 cps

examinations was carried out with a contour type mask for the flash lamp, which controlled ambient light, and the lamp-eye distance at 8 to 8.5 cm. The frequency series included 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, and 30 cps. Variable stimulation was omitted in as much as it gave no additional information in the first series. Also studied by this method were 31 normal controls. Control subjects were hospital personnel and students without a history of neurologic disorder. Average age of the 121 control subjects was 27, with a range of 20 to 60 years.

Electroencephalograms were obtained with a Grass Model IIID electroencephalograph in the routine manner, scalp-ear recording with bilateral frontal, central, occipital, and left temporal derivations being utilized during photic stimulation. Eyes were closed throughout the procedure.

Photoconvulsive responses (Fig. 1) were identified by bilaterally synchronous spike and wave activity of 2 to 6 cps, either generalized or with emphasis in central regions, occurring at a slower rate than the stimulus frequency. Photomyoclonic responses (Fig. 2) were recognized primarily by recruiting muscle spikes and movement artifacts, rhythmically related to the stimulus frequency, occurring in the electroencephalogram, particularly in frontal derivations, and secondarily by direct observation of facial, head, and extremity movements. Muscle spikes in excess of 50 μv. in frontal leads were required, thus eliminating mild and equivocal responses. Not included were such responses as immediate voluntary withdrawal and nonrecruiting "blink" responses to slowly repeated flashes of light. An earlier analysis[19] of photic response data revealed that 17 of 53 (32%) normal control subjects gave the latter type response. High amplitude ($>$ 50 μv.) delta and theta responses to frequencies above these ranges and spikey patterns without definite spike and wave characteristics were also tabulated in normal and psychiatric control groups (Fig. 3). These responses were found in 11% of 90 controls and 8% of 133 psychiatric patients. Responses of this nature were excluded from consideration in the present study. The following data were also tabulated for each patient: [1] age, [2] sex, [3] final or interim diagnosis, [4] description of spells including special attention to alterations of consciousness and classical features of the various seizure types, [5] history of alcoholism or drug addiction, [6] family history of seizures, [7] previous electroshock or insulin therapy or frontal lobotomy, [8] major neurologic signs,

[9] ocular findings, [10] psychologic test results, [11] spinal fluid measurements, [12] blood bromide levels, and [13] medications. Psychiatric diagnoses included those in the psychotic, neurotic and character disorder groups only. The chronic brain syndrome category also included patients diagnosed as having arteriosclerotic encephalopathy.

RESULTS

During the initial series of 1,143 patient examinations with the 15-cm. lamp distance, 27 patients were found to exhibit photoconvulsive or photomyoclonic responses or both; 29 were found during the second series of 1,105 examinations with the 8.5-cm. distance. Of the 29 in the second series, 2 were examined more than once; 1 had a photomyoclonic response on 2 occasions, and the second had a photoconvulsive response during 3 successive examinations. The incidence of photoconvulsive and photomyoclonic responses was slightly but not significantly higher in the second series. In the initial series of 90 normal control subjects, 3 met the criteria for photoconvulsive and 2 for photomyoclonic responses; no such responses were elicited from the 31 controls tested with the contour mask. The over-all incidence of 4.1% in our normal series compares with a 3.9% incidence of abnormal "polyspike or wave-spike" responses in Mundy-Castle's[20] young adult normal sample. Ulett,[21] using slightly different criteria of abnormality, has reported that 4.4% of young normal adults exhibit "extreme or paroxysmal" activation.

The clinical findings in 54 patients with atypical photic responses and complete inpatient hospital files are contrasted in Tables 1, 2, and 3 with those of 100 inpatient controls selected alphabetically. Patients with photoconvulsive responses alone or in association with photomyoclonic responses had seizures significantly more often than the patient controls ($X^2 = 26.5$, $p < .01$, and $X^2 = 7.1$, $p < .01$, respectively). If all patients with photomyoclonic responses were contrasted with the patient control group, photomyoclonic responses were also found to relate significantly to convulsive disorder ($X^2 = 12.5$, $p < .01$). The relationship between photomyoclonic responses alone and seizures could not be satisfactorily tested because of the small size of the group. The percentage of patients with convulsions was slightly higher in this group than in the patient control sample. Photomyoclonic and photoconvulsive responses were not significantly associated with unidentified spells, psychiatric diagnosis, or alcoholism. Patients with a history of electroshock or insulin therapy were few and not significantly different in the 4 groups; 3 patients with known drug addiction were included, 1 without a hyperactive response and 2 with photoconvulsive responses.

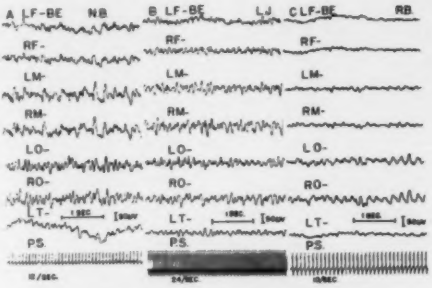

Fig. 3. Examples of dysrhythmic responses not classified as photoconvulsive because of the absence of clear spike-wave characteristics. These occur relatively frequently in nonepileptic samples.

TABLE 1.

PHOTIC RESPONSE CATEGORIES vs. NUMBER PATIENTS WITH CONVULSIVE DISORDER AND UNIDENTIFIED SPELLS

	No hyperactive response (100)		*Photoconvulsive (26)*		*Photoconvulsive and photomyoclonic (12)*		*Photomyoclonic (16)*	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Convulsive disorder	18	18	18	69	8	67	6	37
Unidentified spells	15	15	4	15	1	8	2	13

TABLE 2.

PHOTIC RESPONSE CATEGORIES vs. NUMBER PATIENTS WITH PSYCHIATRIC DISORDER AND HISTORY OF ALCOHOLISM

	No hyperactive response (100)		*Photoconvulsive (26)*		*Photoconvulsive and photomyoclonic (12)*		*Photomyoclonic (16)*	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Psychiatric diagnosis	43	43	8	31	3	25	6	37
Alcoholism	41	41	11	42	8	67	6	37
With seizures	9	9	7	27	5	42	4	25
Without seizures	32	32	3	12	3	25	1	6

TABLE 3.

PHOTIC RESPONSE CATEGORIES vs. NUMBER PATIENTS WITH ACUTE AND CHRONIC BRAIN SYNDROMES

	No hyperactive response (100)		*Photoconvulsive (26)*		*Photoconvulsive and photomyoclonic (12)*		*Photomyoclonic (16)*	
	Number	*Percent*	*Number*	*Percent*	*Number*	*Percent*	*Number*	*Percent*
Acute brain syndrome	7	7	3	14	1	8	3	19
Chronic brain syndrome	24	24	7	27	2	17	8	50
With seizures	4	4	3	12	1	8	3	19
Without seizures	20	20	3	12	1	8	4	25

Medications were known for all patients; 3 (6%) with and 14 (14%) without hyperactive responses were receiving Thorazine, and 5 additional patients without hyperactive responses were receiving other tranquilizing agents. Fewer patients with convulsive disorders who had photoconvulsive responses were receiving either Dilantin or phenobarbital or both (28%) than those who did not (56%). It is thus possible that the photoconvulsive response was pharamacologically suppressed in individual cases in the latter group.

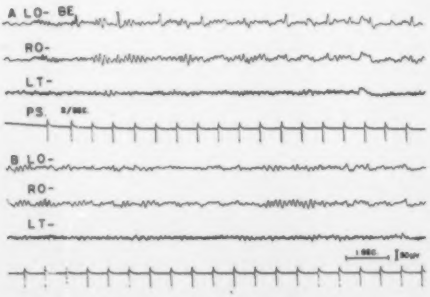

Fig. 4. Focal spikes elicited by slowly repeated photic stimuli. A and B are continuous. Note early alternation and later lack of response.

A case of some interest not included in the tabulation was a 61-year-old hypertensive male in whom focal spikes could be repeatedly evoked in the left occipital region with slow frequencies of stimulation (Fig. 4). During this initial electroencephalogram, focal spikes occurred only twice during the resting tracing (twenty-one minutes of recording). Other evidence of focal dysfunction was minimal, low amplitude asymmetric delta formations appearing only rarely. Focal spikes were also evoked during examinations two and thirty days later but with less consistency. Seven days before the first electroencephalogram, the patient complained that he was "unable to see" and was observed to be confused. A coarse nystagmus with the fast component to the right was noted. Subsequently, he had irregular jerking movements of the right arm associated with stiffness of both legs. Neurologic signs were fleeting and not consistently lateralizing. A

pneumoencephalogram revealed minimal bilateral dilation of the lateral ventricles. One month after the first attack, the patient had a generalized seizure that began on the right side. No further attacks were recorded during the next four months. Although the evoked discharges in this individual were suggestively paroxysmal and the clinical attacks were presumably convulsive in nature, it was felt unwise to term this particular response photoconvulsive because similar lateralized abortive spike and wave forms occur not uncommonly to slow frequencies of stimulation in patients with cerebrovascular accidents without seizures.[1,2]

No correlation with seizure type emerged, the vast majority of these patients having major seizures (29 of 32) either alone or in association with petit mal or psychomotor attacks. Diagnoses of convulsive disorder had not been made in 12 patients with photoconvulsive responses; 5 of these had a history of possible seizures, although the description of the spell was not sufficiently characteristic to permit a positive diagnosis. The diagnoses in the remaining 7 cases were chronic brain syndrome with cerebral arteriosclerosis (2), chronic brain syndrome with central nervous system lues (1), posttraumatic encephalopathy (1), schizophrenia (2), and acute brain syndrome due to alcohol (1). Both patients with schizophrenia had had electroshock and insulin shock therapy, and 1 had had bilateral prefrontal ultrasonic lobotomies.

In order to find out how often these abnormal responses occur in an epileptic sample, all patients discharged from the hospital between March 1954 and December 1958 with a diagnosis of convulsive disorder were listed. Of this group of 153 patients, 20 (13%) had hyperactive responses, which were categorized as photoconvulsive in 12, photomyoclonic and photoconvulsive in 6, and photomyoclonic in 2. All but 2 of the 20 had major seizures. Typical bilateral photoconvulsive responses were found in 1 patient with jacksonian attacks and another with psychomotor seizures. Average age in this sample was 40, with a range of 25 to 73 years. A comparative group of 100 psychiatric patients, 50 psychotic and 50 nonpsychotic, included only 2 patients with atypical responses of these types, 1 having

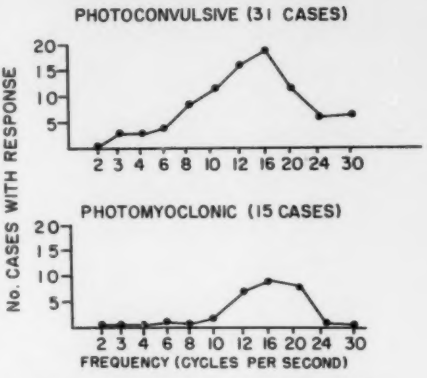

Fig. 5. Frequency of stimulation vs. incidence of photoconvulsive and photomyoclonic responses

both photoconvulsive and photomyoclonic elements and the other photomyoclonic alone; 13 of these patients had had previous electroshock or insulin therapy. Average age of the sample was 42, with a range of 22 to 67 years.

Effectiveness of the various frequencies in evoking photoconvulsive and photomyoclonic discharges is graphed in Figure 5. The series was incomplete in 7 patients with photoconvulsive responses and 13 with photomyoclonic responses, photic stimulation being terminated in order to avert a possible seizure. These cases are not included. Clinical seizures have occurred in only 2 instances with our technic. In both cases, these resembled protracted petit mal attacks, the patients being unresponsive and exhibiting fluttering of the eyelids and staring. The electroencephalograms during the attacks were characterized by generalized 2- to 4-cps multiple spike and wave discharges.

In 23 of the 38 instances of photoconvulsive responses, the resting electroencephalogram gave no evidence of paroxysmal activity, that is, spikes or spike and waves. In the remainder, photic stimulation exaggerated preexisting paroxysmal signs. If the paroxymal discharge appeared only coincidental, the patient was not included in the series.

DISCUSSION

The finding of photoconvulsive and photomyoclonic responses in normal control subjects and psychiatric patients indicates the need for

caution in the clinical interpretation of such responses. However, the data presented support the hypothesis that the photoconvulsive response, as elicited with the technic used in the present study, is suggestive evidence of a convulsive tendency. On the other hand, photomyoclonic responses appear to have little specific value. The finding of an increased percentage of patients with acute or chronic brain syndromes in the group with photomyoclonic responses is of interest and may be worth further study.

The incidences of photomyoclonic and photoconvulsive responses were not significantly different in 100 randomly selected hospitalized psychiatric patients and 121 control subjects. Furthermore, patients with psychiatric diagnoses appeared less often in the atypical response group than in a random laboratory patient sample. Thus, these findings do not give additional support to results of previous investigations which indicate a relationship between abnormal responses to photic stimulation and psychiatric disease (see reviews by Bonnet and Bonnet[15] and Ulett[21]).

It might be reasonably expected that epileptic patients with photoconvulsive responses to photic stimulation would represent cases of photogenic epilepsy clinically. Light-sensitive epileptic patients have been frequently observed since the original descriptions of Gowers.[22] On the other hand, it is worthwhile to point out, along with Daly and Bickford,[23] that a history of photosensitivity is often unobtainable, even with the most careful questioning, and one of our patients with typical bilaterally synchronous spike and wave responses had seizures only during sleep.

That both photoconvulsive and photomyoclonic responses not uncommonly occurred in a single subject suggests a relationship between the two phenomena. The exact nature of the relationship is uncertain. Considerable independence of the responding systems can be predicated on the basis of instances in which only one of the response patterns emerge, the differential motor and sensorial concomitants, and the frequent lack of temporal association between the responses even when both occur in the same individual. The photoconvulsive response also appears to be more closely related to the mechanism of the convulsive seizure than the photomyoclonic. Rather than postulating a causal relationship, we feel that activation by photic bombardment may proceed relatively independently within the two systems initially. Both may be activated or only one, depending upon the functional state of each system. Later, with progression of the response, spread may occur to other neural arcs subserving sensorial or additional motor functions. The photoconvulsive response appears to signal a disruption of neural events in that system associated with higher integrative functions; the photomyoclonic response may represent an alteration of neural activity in centers and arcs responsible for optic protective motor functions. In the former case, the diffuse thalamic projection system presumably plays an important role.[24] The neuroanatomic substrate of the photomyoclonic response has not been fully elucidated. The facts that the response is involuntary and the muscles involved are similar to those responding in the "blink" and related motor reflexes[25] suggest that the altered functional state exists largely within this reflex system. The relative importance of cortical, thalamic, and brain stem circuits remains problematic. The studies of Gastaut and Hunter[26] and Lorentz de Haas, Lombroso, and Merlis[27] on the effect of ablation of motor and visual cortices on the photically evoked myoclonic response in the Metrazolized cat are of interest in this regard. Ablation or freezing of the motor cortex did not abolish the response. The latter authors reported further that a response could be obtained even after complete decortication. However, they noted that the Metrazol thresholds were raised with both motor cortex ablation and decortication, indicating that the motor cortex may play a facilitatory role. It should be pointed out that these experimental myoclonic responses are to single light flashes and are accompanied by a spike discharge that can be recorded at the cerebral surface. These differences may make the results not strictly applicable.

The findings obtained relating frequency of stimulation to incidence of evoked photoconvulsive and photomyoclonic discharges parallel those of earlier investigations.[9,11,28,29] The special efficacy of frequencies in the 10- to 20-per-second range has been discussed in re-

lation to the normal cortical excitability cycle by Gastaut and associates.[30] Our case in which spikes could be evoked in the left occipital region (Fig. 4) deserves further mention in this regard inasmuch as the suggestively paroxysmal formations were evoked maximally with frequencies of 0.5 to 3 per second, frequencies in the 10- to 20-per-second range being without significant activating properties. This patient followed the pattern of frequency specificity that was observed in experimental animals with light-sensitive epileptogenic lesions resulting from the injection of penicillin in the visual cortex of cats.[31] Rodin, Daly, and Bickford[32] have reported on 2 epileptic patients with occipital foci in whom the response to photic stimulation also appeared to follow this pattern, sharp waves being evoked by frequencies slower than 6 per second. Thus, it is likely that 2 types of physiologic mechanism underlying light-evoked paroxysmal formations can be differentiated on the basis of frequency response.

SUMMARY AND CONCLUSIONS

Intermittent photic stimulation was carried out during 2,248 examinations of patients routinely referred to the electroencephalographic laboratory; 121 normal control subjects were also studied. With the parameters of stimulation employed, the incidences of photoconvulsive and recruiting photomyoclonic responses were low in both patient and control samples.

Comparison of patients with and without hyperactive responses indicated that photoconvulsive responses were highly suggestive of convulsive tendency. Convulsive seizures in patients with photoconvulsive responses were not necessarily light-evoked.

Photomyoclonic responses may be associated with photoconvulsive responses. The likelihood of convulsions was also high in these patients.

If only a recruiting photomyoclonic response was identified, the possibility of the patient having a seizure disorder was slightly increased over that in a random laboratory sample. The predictive specificity of the photomyoclonic response appears low in relation to the factors studied.

The authors wish to extend their appreciation to Dr. Reed S. Boswell for statistical advice and to Miss Ruth Rowe and Mr. Raymond Cooper for invaluable technical assistance.

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A POSTGRADUATE COURSE in Clinical Neurology will be given March 13 and 14, 1961, at the University of Michigan Medical Center, Ann Arbor. The course will be presented by Dr. Russell N. DeJong and the staff of the Neurology Department. Program and application form may be obtained from the Department of Postgraduate Medicine, University Hospital, Ann Arbor.

Spontaneous spinal extradural hematoma

W. M. Lougheed, M.D., and H. J. Hoffman, M.D.

THE SYNDROME of spontaneous spinal extradural hematoma has been a rather rare entity. Frequently the lesion is undiagnosed. This has dire consequences, for it is a lesion which must be dealt with early to prevent permanent and total paraplegia.

The first major paper on this syndrome, written by Schultz and associates, appeared in the *Journal of Neurosurgery* in November 1953.[1] They found 12 cases in the literature and added 4 cases of their own. They summarized the syndrome [1] as usually occurring in adults without sex predominance and [2] as being frequently preceded by a history of trauma. Severe neurologic impairment involving any cord segment could occur within twenty minutes after the onset of symptoms, or could take several weeks to develop. In some cases, single or multiple attacks of back and radicular pain without neurologic deficit preceded the final attack by months or years.

Recently, Lowrey[2] added 3 of his own cases, plus 5 others reported since 1953, to the 16 cases collected by Schultz. His findings agreed with those of Schultz and associates. Almost invariably, the initial symptom was pain at the level of hemorrhage, followed within hours or weeks by varying degrees of motor and sensory paralysis. He found that weakness was sometimes delayed in onset and then rapidly became progressive. In other cases, it was slower in progression; occasionally it was intermittent.

Ainslie[3] reported 3 cases (2 of these had been reported by Schultz and were also included in Lowrey's summary). His patients were past 60, were hypertensive, and had experienced a sudden onset of severe pain succeeded by paraplegia. There was no history of trauma or severe effort. The pain was localized in the spinal column at the site of the maximum hematoma. Lumbar puncture showed a complete or incomplete block with high protein and red cells. The myelogram showed an irregularity of the oil column.

A twenty-sixth case, reported by Svien,[4] showed myelographic findings compatible with an intramedullary tumor.

CASE REPORTS

Case 1. This 33-year-old man had been having recurrent attacks of pain between his shoulder blades for approximately five years. Initially these attacks were quite mild and of short duration. However, two years before admission, an attack of severe pain had occurred after he lifted a 200-lb. weight; the pain was between his shoulder blades and radiated about his left anterior chest. This subsided after twenty-four hours. He had a similar severe attack six months before his admission to the hospital. This attack again followed the lifting of a heavy article and again disappeared spontaneously after twenty-four hours. In none of these attacks was there any neurologic deficit.

Two days before admission, while carrying a light but awkward article with the help of another man, he suddenly developed severe pain between his shoulder blades. Within a few minutes his legs became weak; within half an hour they were paralyzed and numb. The pain in his back continued.

Physical Examination. He was transferred to the Toronto General Hospital two days after the onset of his paraplegia. Physical examination on admission showed him to be in excellent health with a blood pressure of 120/80. He had a complete flaccid paralysis of his abdominal muscles and of both lower limbs. He had loss of sensation to pin prick below T5. Sensation to touch below this level was impaired but present. Vibration sense was present at his left but not his right medial malleolus, and position sense was absent in both toes. He had no sensation in bladder or bowel.

Investigation. A myelogram was done. There was a slowing of the passage of oil at the T3—4 level. The oil column formed 2 thin channels at this level and the spinal cord appeared enlarged.

Operation. Three days after the onset of his paraplegia, a laminectomy was performed. Profuse bleeding was encountered and an extradural clot was discovered which extended between T3 and T6. Histologic examination showed a clot and nu-

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Fig. 1 *(Case 1).* Histology of extradural clot

merous large veins that contained very little muscle and had thick fibrous walls (Fig. 1).

Postoperative course. The patient slowly and steadily regained both motor power and sensation. A year postoperatively he was walking without support but with a somewhat spastic gait. Bladder and bowel function were excellent. His legs were spastic and he had complete return of sensation. He had returned to work and was getting along well.

Case 2. This senile 74-year-old woman suddenly developed agonizing, knife-like, nonradiating low back pain. The pain continued steadily for thirty minutes and then gradually disappeared. Twelve hours later she noted a slight numbness in her feet. Twenty-four hours later there was weakness in her lower extremities and she fell on getting out of bed. Thirty-six hours later she became completely paralyzed in both lower limbs and was unable to void.

Physical Examination. The patient was admitted to another hospital five days after the onset of her pain. Physical examination there showed her to be having auricular fibrillation with a blood pressure of 180/120. She was tender over L2, 3, and 4. She was paraplegic below L1. Lumbar puncture showed xanthochromic fluid. Eight days after the onset of her pain, the patient was transferred to the Toronto General Hospital. Examination at that time disclosed weakness of the lower abdominal muscles and no movement in either leg. The lower limbs were flaccid and areflexic except for a minimal left knee jerk. There were no abdominal reflexes and the left toe was upgoing. There was an equivocal right plantar response. She was anesthetic below L1 except for some minimal perianal sparing of sensation to pin prick.

Investigation. A lumbar myelogram was attempted. However, it was not possible to place oil in the subarachnoid space by this method. Consequently, a cisternal puncture was done. It showed a partial obstruction to the flow of oil in the thoracic region which extended between D8 and L1. There was separation of the oil column into 2 lateral gutters. The spinal canal did not appear widened, which suggested that the lesion was extradural, not intramedullary.

Operation. Ten days after the onset of the patient's pain, laminectomy was done. An extradural hematoma was found extending between T10 and L1. No pathologic lesion could be found to account for this hemorrhage.

Postoperative course. The patient had some return of motor power in her lower extremities. This was especially true of her left lower limb, where she developed good movement in her hip and knee. However, rehabilitation was found to be impossible in this patient because of her senility and mental confusion.

Case 3. This 67-year-old retired hypertensive male suddenly awoke with low back pain and pain down both legs to his feet. This pain continued steadily. Five hours later, when he tried to get up from bed, he found that his legs were profoundly weak.

Physical Examination. When seen twelve hours after onset of his symptoms, he was found to be incompletely paraplegic below T12. There was a flicker of movement in his left quadriceps and in the toes of both feet. His abdominal reflexes were present. Knee, ankle, and plantar responses were all absent. Sensation to pin prick and light touch was almost completely absent over L3 to L5, but there was sparing of sensation over the sacral segments bilaterally. His blood pressure was 220/105.

Investigation. Plain x-rays of the thoracolumbar spine showed only some degenerative changes. It was found to be impossible to get into the subarachnoid space by lumbar puncture and so a cisternal puncture was done. A myelogram disclosed a complete block at T12. The appearance of the myelogram was very suggestive of an intramedullary lesion.

Operation. An immediate laminectomy was performed. This showed a recent extradural clot about ½ in. in thickness extending from T11 to L5. Postoperatively, he made a most gratifying recovery; six weeks postoperatively he had return of normal function in his legs.

Case 4. This 57-year-old male printer had a three-month history of occasional dull low back pain occurring at rest and relieved by walking. Five days before admission to the hospital, he suddenly awoke in the night with severe epigastric pain. Within a matter of minutes, he found that his legs were numb and weak with the level of numbness ascending to his lower ribs. During the next few minutes his legs became completely paralyzed. He was seen by the family physician at home, was given a sedative, and in the course of the next few hours the function in his legs returned. Twenty-four hours after this episode he returned to work and worked one day. Fifty-six hours after his initial episode, he was awakened by severe pain between his shoulder blades. Within half an hour, his legs were weak and numb.

During the next half hour, his legs became completely paralyzed and he became numb up to his nipple line.

Physical Examination. On admission, physical examination showed him to be completely paraplegic below T6. His blood pressure was 150/80.

Investigation. Plain x-rays of his dorsal spine were normal. A lumbar puncture was done. The fluid was clear and colorless with a protein of 73 mg. per cent. The myelogram showed an extradural defect in the oil column extending from T3 to T5.

Operation. Ten hours after his last episode, a laminectomy was performed at T3 to T5, and an extradural clot was found. This was ½ in. long and ¼ in. thick; it lay on the dorsal and right lateral aspect of the dura. A large vein was seen running over the surface of this clot. Pathologic examination showed no evidence of vascular malformation.

Postoperative course. The patient made a very slow recovery. In the course of the next several months, he reached the stage where he was up and walking with the help of braces.

Case 5. This 54-year-old woman suddenly awoke with severe pain between her shoulder blades. The pain subsided in fifteen minutes but was soon followed by numbness and paralysis of her legs. Approximately six hours after her initial pain, she developed more pain between her shoulder blades and her numbness ascended to the nipple line. She became incontinent of urine and feces.

Examination. Examination on admission showed her to be completely paraplegic below T5. Otherwise, she was in excellent health; her blood pressure was 125/80.

Investigation. Investigation included x-rays of her cervical and thoracic spine, which were normal. Lumbar puncture was done. The fluid was grossly bloody and had a protein of 108 mg. per cent. A myelogram revealed no evidence of block or of extrinsic pressure on the cord.

Operation. Because of the grossly bloody spinal fluid and the failure to demonstrate any abnormality in the myelogram, it was thought that this patient had experienced a spinal subarachnoid hemorrhage from a malformation. However, when there was no recovery of function four days after the onset of her symptoms, it was decided that she should be explored. A laminectomy was done between T5 and T10. An extradural clot ¼ in. in thickness, lying dorsal and lateral to the cord in the extradural fat between T5 and T10, was removed (Fig. 2).

Postoperative course. There was no change in the patient's level of cord injury and she remained completely paraplegic.

Case 6. This 55-year-old Chinese cook had a five-year history of intermittent low back pain and pain in both buttocks and down the lateral aspect of both thighs. This was never severe and was usually associated with cold weather. For a year before his present admission to the hospital, he

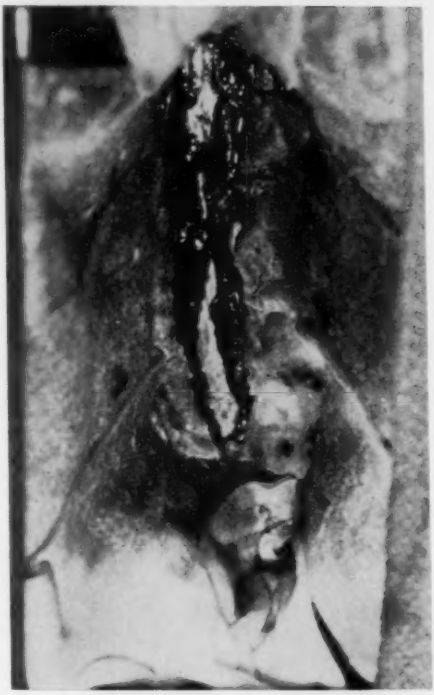

Fig. 2 *(Case 5).* Appearance of the extradural hematoma at operation

was troubled with angina pectoris. He was noted to have a blood pressure of 220/105 and was placed on treatment with Serpasil. Because of his angina he retired from work.

While sawing lumber, he had a sudden onset of severe subcostal pain with pain in his lumbar spine and down the back of both legs. Within half an hour, both legs were numb and paralyzed. When seen by his family physician one and one-half hours after the onset of the pain, he had a flaccid paralysis of both legs and was anesthetic to within 1 in. below his umbilicus. His back and leg pain continued unabated. However, twelve hours after the onset he began moving his right knee.

Examination. On admission to this hospital twenty-four hours after onset of symptoms, his blood pressure was 160/90. He was tender over his lumbar spine. There was a suggestion of nuchal rigidity. Both his lower limbs were flaccid with absent reflexes. However, his abdominal reflexes were present. He had about grade 2 power in the muscles about his right hip and right knee and grade 1 power in the muscles about his left hip and left knee. Sensation to light touch and pin

Fig. 3. Myelogram in Case 6. The oil was introduced through a cisternal puncture. A complete block is shown at T12; the myelogram gives the appearance of a widened cord, which is suggestive of an intramedullary lesion.

prick was reduced over his lumbar dermatomes and lower sacral dermatomes bilaterally and was absent over S1 bilaterally.

Investigation. A lumbar puncture was attempted shortly after admission. However, there was great difficulty in entering the subarachnoid space and only a small amount of fluid could be obtained. This was found to be grossly bloody. On the day after his admission, a myelogram was attempted via the lumbar route; it was impossible to inject any oil into the subarachnoid space.

It was thought at this time that the patient had probably had a spinal subarachnoid hemorrhage. This belief was based on the grossly bloody spinal fluid and the patient's improvement in neurologic status. However, on the following day no further improvement was noted in his neurologic signs. Therefore, a cisternal puncture was performed and a myelogram done. This myelogram showed a complete block at T12 and gave the appearance of an intramedullary lesion (Fig. 3).

Operation. A laminectomy was performed immediately after the myelogram. At this time, approximately seventy-two hours had elapsed since the onset of his symptoms. At operation, an extensive extradural clot was found lying dorsal to the cord and extending between T11 and S1. It was thickest at L1–2; at that point it was approximately ½ in. thick.

Postoperative course. The patient did very well. Four weeks postoperatively the power in his right leg ranged from grade 3 to grade 3½ and the power in his left leg was between grade 2 and grade 2½. There had been a steady rate of improvement in sensation. Sensation was reduced only over the sacral dermatomes; and it was present over the lumbar dermatomes.

DISCUSSION

Twenty-six previously reported patients with spontaneous spinal extradural hematoma are listed and 6 new patients with this condition are reported. The 6 newly reported cases are not associated with trauma; 3 of the patients were sleeping at the onset of their symptoms, and 2 patients were performing their usual work. Only in 1 case is there any pathologic evidence of a vascular malformation. It is to be expected, however, that if all clot material had been saved and serially sectioned, abnormal vessels would have been found more frequently; this was demonstrated by Woodhall[5] in cases of small atrioventricular malformation.

A significant feature seems to be the dorsal location of the hematomas, and the fact that this location can cause a central indentation of the dural sack. The indentation then produces the picture of intramedullary lesion on the myelogram, as happened in the case of 3 patients reported here and in the case reported by Svien.[4] Occasionally, the myelogram fails to demonstrate a clot, as occurred in Case 5 and in Sadka's 2 cases.[6]

Another important feature is the difficulty encountered in spinal puncture when the hemorrhage is in the lumbar region. This may obscure the diagnosis by suggesting either traumatic tap or subarachnoid hemorrhage. When

the clinical features point to lumbar involvement, a cisternal puncture and myelogram should be carried out. The importance of early laminectomy is demonstrated in these cases. For example, the patient in Case 3 was operated on only sixteen hours after the onset of symptoms; he then went on to complete recovery.

These cases exemplify the points that have been stressed in the past. The patients are frequently in the older age group and they are frequently hypertensive. The clot may occur in any segment of the extradural space. Symptoms begin with sudden severe pain that is localized to the area of the clot, usually with radicular radiation; paraplegia follows shortly. In 3 of the cases, there was a history of occasional back pain for some time preceding the acute episode.

SUMMARY

Six cases of spontaneous extradural hemorrhage have been added to the 26 cases previously reported. The case histories and myelographic and operative findings are recorded. Early recognition and prompt surgical treatment are stressed. It is suggested that vascular abnormality is the basis for this hemorrhage, although the abnormality is frequently missed because of incomplete collection and sectioning of the clots.

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Abnormal protein fractions of cerebrospinal fluid demonstrated by starch gel electrophoresis

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SPINAL FLUID PROTEINS have been examined by a variety of methods in the hope that demonstration of changes in their quantity, composition, and properties might be helpful in clinical diagnosis and might give some insight into the mechanism of the disease processes. The higher the sensitivity or resolving power of a given method, the finer the changes that can be detected. We selected starch gel electrophoresis for our study because of its exceptional resolving power.

Zone electrophoresis in starch gel with borate buffers was introduced by Smithies in 1955[1] for examination of serum proteins. This method has been modified in our laboratory to adapt it to the smaller amounts of protein usually available in spinal fluid samples.[2] With this technic, 10 to 12 fractions are ordinarily seen but, occasionally, additional fractions also appeared which were designated as "fast gamma" and "additional prealbumins." Since the publication of the adaptation of the method for spinal fluid protein electrophoresis and preliminary results, more spinal fluid samples have been examined, more changes noted, and improvements in the procedure devised.

METHOD AND MATERIALS

Most patients from whom spinal fluid was obtained suffered from neurologic disorders.

The technic for starch gel electrophoresis used in this laboratory has been previously described.[2] The technic of concentration of spinal fluid has been altered for this study. Collodion bags were used instead of cellophane bags and negative pressure[3] instead of polyvinyl pyrrolidone because the loss of proteins and lipoproteins in collodion bags proved to be smaller than that by the cellophane bag technic. The quantity of spinal fluid used is selected according to the total protein content because it became obvious that the quantity of proteins in relation to the cross-sectional area of the gel could vary only within narrow limits if optimal resolution were desired. The cross-sectional area of strips presently used (5 x 7 mm. and 200 mm. long) gives good resolution of protein in amounts of 1.5 to 4 mg. To demonstrate a minor fraction, optimal resolution of other fractions is at times sacrificed and larger amounts of spinal fluid are used.

The concentrated spinal fluid is placed in a slit 1 mm. in width in a gel block prepared from commercial prehydrolyzed starch according to the instructions of the manufacturer (Connaught Medical Research Laboratories, Toronto). The electrophoresis runs were performed in a low-temperature incubator (Assembled by Canal Industrial Corporation, Bethesda, Md.) at +9° C. for five hours. After completion of the run, the gel strips are stained with napthalene black B for proteins. The detection and assaying of proteolytic enzymes in the eluate of the protein fractions was carried out as previously described by Chap-

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man and Wolff.[4] The technic is based on the observation that certain proteolytic enzymes form a polypeptide (bradykinin) when mixed and incubated at 37° C. for three minutes with 1% solution of globulin (Fraction II, Nutritional Biochemical Corporation). The formation of bradykinin is then assayed with a smooth muscle preparation.

In the description of the patterns, terms referring to the classical electrophoresis nomenclature are used when applicable; otherwise, the authors' descriptive designations are used.

RESULTS

The table lists some of the abnormal protein fractions found with the disease states encountered in the patients studied. The large number of cases of multiple sclerosis, diabetes mellitus, and cerebrovascular accident reflects our interest in these diseases. The most commonly observed pattern of the spinal fluid proteins in persons with and without clinically demonstrable nervous system or systemic disease is shown in Figure 1. Variations in the arrangement of the intermediate bands are observed in that there can be several smaller bands instead of the band marked B and that the band marked A can show marked variations in intensity. With some disease states involving the nervous system, additional bands are seen and have been designated "fast gamma," "gamma proper-2," and "additional prealbumins" (Fig. 2). Also, a selective relative increase in the intensity of the slowest band migrating toward the anode (probably consisting of slow alpha-2 globulins) may occur (Fig. 3).

Frequently encountered with a wide variety of neurologic and psychiatric disorders, although not in each individual patient, is a sharp, narrow band migrating toward the cathode, as seen in Figure 2A. This band has been designated "fast gamma." Its magnitude did not seem to be necessarily proportional to the amount of gamma proper. The fast gamma band was observed with diseases such as amyotrophic lateral sclerosis, cerebral vascular accidents, multiple sclerosis, and brain tumors (see table). It was seen also in states without well-defined or accepted gross structural pathologic changes, such as idiopathic epilepsy, schizophrenia, and vascular headaches.

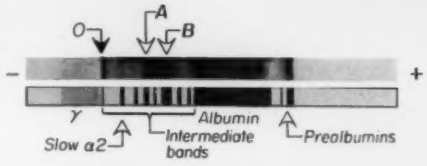

Fig. 1. The most commonly seen spinal fluid protein pattern. Frequent variations in this pattern include changes in the magnitude of the band marked A or a splitting of the band marked B into several small bands. 0 marks the site of application of 1.5 mg. of protein.

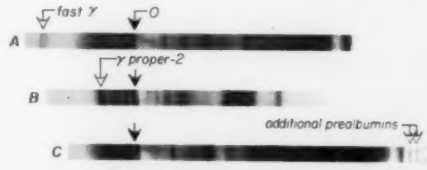

Fig. 2. Starch gel electrophoresis runs of cerebrospinal fluid proteins. [A] Fast gamma: 4 mg. of protein applied from a patient with a metastatic brain tumor. [B] Gamma proper-2: 1.5 mg. of protein applied from a patient with multiple sclerosis. [C] Additional prealbumins: 8 mg. of protein applied from a patient with acute bacterial meningitis. 0 marks the site of application. On this photograph, the additional prealbumin bands have been intensified for clearer visualization.

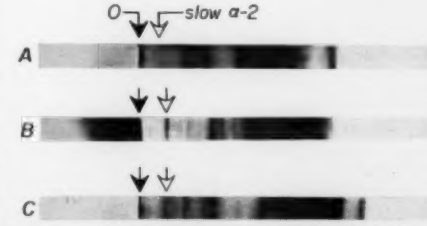

Fig. 3. [A] Commonly seen spinal fluid protein pattern (1.8 mg. of protein applied). [B] Normal human serum protein pattern from same patient. [C] Spinal fluid pattern of a patient with cerebral arteriosclerosis (2 mg. of protein applied). The band marked slow alpha-2 is prominent in normal serum [B] and in spinal fluid from the patient with arteriosclerosis [C].

DISEASE STATES AND SOME OF THE ABNORMALITIES ENCOUNTERED IN PATIENTS INCLUDED IN THIS STUDY

	Number of patients	Incidence of abnormalities			
		Fast gamma	Gamma proper-2	Additional prealbumins	Increased slow alpha-2
Amyotrophic lateral sclerosis	5	2	0	0	0
Brain tumors					
Primary	9	1	0	0	8
Metastatic	14	3	1	0	5
Cerebellar degeneration	6	1	0	0	0
Cerebrovascular accidents	22	4	0	0	15
Central nervous system lues	7	0	0	0	2
Diabetes					
Uncomplicated	11	1	0	0	0
With neurologic dysfunction and/or arteriosclerosis	32	8	0	0	21
Degenerative central nervous system disease of unknown origin	8	1	0	0	0
Extrapyramidal disease	9	0	0	0	2
Guillain-Barré	2	1	0	0	0
Liver cirrhosis	4	0	0	0	0
Meningitides	7	3	1	3	5
Metastatic malignancies	14	3	0	0	1
Migraine	3	1	0	1	0
Multiple sclerosis	42	10	11	0	1
Nutritional neuropathies	8	2	0	0	0
Schizophrenia	26	17	0	0	2
Seizure disorders of unknown origin	17	3	0	0	2
Undiagnosed nervous system disease	16	6	0	0	2
No obvious nervous system disease	11	0	0	0	0

The fast gamma fraction was eluted from the gel block by freezing the entire strip, cutting out the section containing the fast gamma, thawing this section, and compressing it to remove the liquid material. The eluate liberated relatively high amounts of bradykinin from a protein substrate in the range of 100 milliunits per cubic centimeter as defined by Rocha e Silva, indicating proteolytic activity. When the spinal fluid samples that showed the presence of fast gamma were stored in a refrigerator for several weeks or in a frozen state for several months, this band was no longer present or had decreased in magnitude. It is therefore likely that at least one of the proteolytic enzymes of spinal fluid migrates in the fast gamma region. The fast gamma was never observed in the serum of the same patients.

A band in the gamma globulin region seen occasionally at the cathode end of the gamma proper, as shown in Figure 2B, was designated "gamma proper-2." This band was seen in the samples from 11 of 20 patients with multiple sclerosis, all of whom showed a recent or present exacerbation of their symptoms and signs. This band was not seen in fluid from 22 patients with inactive multiple sclerosis. The gamma proper-2 was seen only twice in specimens from 250 patients with diseases other than multiple sclerosis; one patient had cryptococcus meningitis and the other had widespread malignant melanoma. The gamma proper-2 was never demonstrable in the serum of the same patients.

Additional bands were seen in the region of the prealbumins (Fig. 2C) in 3 patients with purulent meningitis; 2 sharp bands were noted in front of the commonly seen prealbumins. These bands are small in magnitude and visible only when 2 to 3 times the optimal amount of protein was applied (4 to 8 mg.), sometimes sacrificing resolution in other areas. They were no longer demonstrable when the

fluids became sterile, although pleocytosis and increase of total protein were still present. We attempted to reproduce these bands by mixing and incubating spinal fluid with bacterial cultures with and without addition of white blood cells. No additional prealbumins developed. It is likely that these proteins are associated with bacteria but can develop only in the subarachnoid space. A wide, diffuse prealbumin band was seen in a spinal fluid sample taken from a patient during an acute attack of migraine headache. The additional prealbumins did not appear in the serum of the same patients.

In spinal fluid, the slowest band migrating toward the anode is not ordinarily very prominent, as can be seen in Figure 3A. In serum, a usually prominent band in a similar location has been identified as slow alpha-2 globulin[1] (Fig. 3B). This band was seen to be relatively increased in magnitude in the spinal fluid of 21 patients with diabetes and vascular disease with or without peripheral nerve dysfunction and in 15 patients with cerebrovascular accidents. It is of interest that this change in spinal fluid protein is always present among other changes when there is an obvious defect in the blood-brain barrier, as occurs with subarachnoid hemorrhage and bacterial meningitis. It is often seen with a suspected defect in the blood-brain barrier, as may occur in highly vascular central nervous system tumors.

DISCUSSION

Our present experience with this method does not allow accurate quantitative assessment of the data from the gel strips, although some progress is being made in this matter by elaborating the scanning devices and standardizing the technics. Our ability to interpret the patterns is in the process of development.

The spinal fluid protein patterns obtained in persons who had no clinically demonstrable nervous system or systemic disease show some variations, but we have observed no additional bands in patients without nervous system disease. It is possible that the protein fractions which we have seen only with disease states also exist in the absence of disease processes but that they exist in such small quantities that the technic used is inadequate for their demonstration. However, we presently believe that, when these fractions appear in amounts large enough to be demonstrable with the technic employed, some alterations in the normal protein metabolism may have occurred. Demonstration of proteins in the spinal fluid which were not seen in the serum of the same patient may indicate that altered protein metabolism in the nervous tissue is releasing products into the spinal fluid. The presence of gamma proper-2 in some active cases of multiple sclerosis and occasionally with other diseases may indicate that development of intermediary products might be similar in different diseases. On the other hand, the absence of gamma proper-2 in some instances of active multiple sclerosis could also indicate that not all patients with the clinical picture of that disease need to have identical mechanisms in the development of the lesions. Finally, a selective increase of proteins in the spinal fluid, such as slow alpha-2 globulin, which is abundant in serum, may indicate a selective or partial defect in the blood-brain barrier. Although the real significance of these protein fractions demonstrated by starch gel is still obscure, the data indicate that further information could be obtained from analysis of spinal fluid protein.

SUMMARY AND CONCLUSIONS

Protein fractions demonstrated by starch gel electrophoresis and designated by us as "fast gamma," "gamma proper-2," and "additional prealbumins" were seen in spinal fluids of patients with disorders of the nervous system. Fast gamma, which was found to be associated with proteolytic activity, was seen with a wide variety of disorders and gamma proper-2 mostly in multiple sclerosis; the additional prealbumins were seen in purulent meningitides. A selective relative increase of slow alpha-2 fractions was seen most frequently in the spinal fluid of patients suffering from sclerosing arterial disease.

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Idiopathic dystonia musculorum deformans

II. The formes frustes

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FORME FRUSTE is a term variously applied to diseases that display [1] short-lived and generally mild manifestations, [2] absent or incompletely developed clinical signs and symptoms deemed characteristic of the condition, or [3] arrest and even remission in the case of notoriously progressive diseases. Obviously, one can speak of formes frustes only in reference to well delineated entities. The first definition is often applied to mild forms of infectious diseases. Here, the alternative term, "abortive form," is probably more pertinent. In hereditary conditions, the second difinition is considered to be the equivalent of low or variable expressivity of the pathogenic genes. Gunther and Penrose[1] have proposed an interesting hypothesis for explanation of such variability of expressivity which might be applicable to the cases of the present study. The third definition applies specifically to the arrested forms of those heredodegenerative diseases in which progression is one of the main diagnostic hallmarks.

Before the existence of formes frustes of dystonia musculorum deformans can be discussed, consideration should be given to whether this condition represents a distinct clinical entity. Wimmer[2] in his report to the Tenth Annual International Neurologic Reunion (1929) argued eloquently against such an assumption. His argument was based chiefly on the consideration that many different pathologic factors such as vascular, traumatic, inflammatory, degenerative, and neoplastic lesions might lead to the syndrome of dystonia. Since then, observation of nonsecondary forms of dystonia permitted the delineation of idiopathic dystonia musculorum deformans as a disease entity.[3]

In a previous report,[4] the authors presented evidence for dominant inheritance with variable expressivity and complete penetrance of dystonia musculorum deformans. The study of Family P., in which the disease had affected 4 consecutive generations, afforded us the opportunity of observing a number of cases in which a diagnosis of formes frustes of dystonia musculorum deformans seemed proper.

Such formes frustes have remained largely unrecognized because the diagnosis of dystonia appeared justified only when "selective systemic symptoms in the form of dystonic movements and postures" are present and when the disease is of "gradual development without recognizable etiologic factors," to quote Herz,[3] an authority on this condition. Comprehensive reviews of the clinical features of dystonia and thorough case studies are readily available. This report, therefore, is limited to a description and discussion of the formes frustes that have so far found little or no attention in the literature.

The pedigree of the family on which this study is based is depicted in the figure. The age indicates either the age at the time of death or the age in 1958, the time of investigation.

Subjects III-10, IV-11, 13, 18, and 19, and V-6 were thoroughly studied in this hospital. III-13 was examined as an outpatient only.

The chief complaints of these 7 patients were dystonic movements in the form of relatively slow, long-sustained, powerful, nonpatterned, contorting hyperkinesias of the axial and appendicular muscles. During sleep and under general anesthesia, the hyperkinesias disappeared. In IV-13, 18 and 19, sustained muscle spasms had led to various contracture deformities such as clubfoot and kyphoscoliosis. These 3 patients are completely helpless and crippled.

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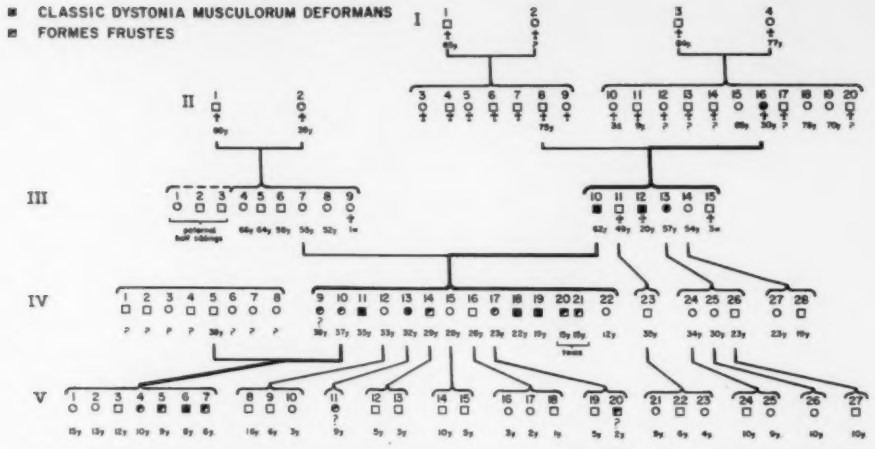

Pedigree of Family P. Question marks designate the most questionable formes frustes. See text.

In all but one patient, the disease developed insidiously during childhood, gait being impaired first. III-13 was allegedly normal until age 23, when she first noticed a drawing sensation in neck and trunk muscles finally leading to a typical spasmodic torticollis. The disease has taken a slowly progressive course over a number of years and seems to be arrested in all but V-6. Dystonic movements and postures have been present for more than fifty years in III-10, thirty-four years in III-13, and twenty-three, twenty-two, fifteen, and fourteen years in IV-11, 13, 18, and 19, respectively.

On physical examination, neurologic deficits were found to be restricted to the above mentioned abnormalities in motor functions. There was no ataxia. Sensory functions were normal. Electromyograms done in 4 patients revealed an almost constant simultaneous innervation of both agonists and antagonists. Electroencephalographic tracings could not be interpreted because of muscle artifacts. Pneumoencephalograms in III-10 and IV-11 were normal except for questionable widening of subarachnoid spaces; however, there was definitely no atrophy of the caudate nuclei. Laboratory examinations including liver function tests, electrolyte studies, endocrinologic studies, serum electrophoresis, and urine paper chromatography for amino acids were all normal. Serum concentration and urine excretion of malic and formic acids as determined by column fractionation were increased in all patients of this family but were within normal range in controls affected with psychogenic hyperkinesias. None of the patients exhibited any abnormal pigmentation or anything suggestive of a Kayser-Fleischer ring.

All affected members of this family were found to be mentally deficient to a moderate degree. Despite their motor disturbances, all patients appear to be healthy in all other respects.

From these observations, it was felt that a diagnosis of idiopathic dystonia musculorum deformans could be definitely made. Huntington's chorea appears to be unlikely because the disease began in all but one patient during childhood and because of the normal pneumoencephalograms. Wilson's disease, in turn, can safely be ruled out because of extremely long duration of the disease, associated with normal liver function, and the absence of aminoaciduria and pigmentation. It was concluded that II-16 and III-12, both of whom were deceased at the time of investigation, were affected by the same condition. This conclusion was supported by the description of the disease symptoms as furnished by the siblings of these two patients.

The following clinical observations were made on members of this family whose symptoms would not be commonly ascribed to dystonia musculorum deformans. Yet the fact that parent, siblings, and/or children of these patients exhibit the classic form of the disease strongly suggests that these cases represent formes frustes of the familial condition.

SYMPTOMS OF THE FORMES FRUSTES

These formes frustes display a rather wide spectrum of manifestations, some of which can be considered as borderline dystonic symptoms such as dyssynergias and certain postural anomalies. Others, however, appear to have no relationship to the disease, for example, tics, simple speech defects, and mental retardation. The major clinical manifestations of the formes frustes seem to fall into the following categories: [1] dyssynergias, [2] postural anomalies and contracture deformities not commonly considered to be dystonic, [3] hyperkinesias and tics, and [4] intellectual impairment. The table shows a further breakdown of these manifestations. Where the relationship of these manifestations with dystonia musculorum deformans is doubtful, the issues involved are discussed in the text and the cases are distinguished by a question mark on the pedigree.

Dyssynergias. In this group belong disturbances of motor function which are not apparent at rest. Neither dystonic hyperkinesia nor posture is seen. Voluntary muscle action, however, reveals a disturbance of muscular synergy. This "action dystonia" ("dystonie d'action" of Bériel[5]) is illustrated by the following cases.

IV-10: This was a 37-year-old female, well built and nourished. She had no dystonic movements; her posture was normal. Neurologic examination revealed brisk muscle stretch reflexes. No pathologic reflexes were elicited. Cranial nerves were intact and cerebellar functions normal. No abnormal pigmentations were found; laboratory studies were all within normal limits.

Upon passive movements of the limbs, the muscle tone initially appeared normal. Then episodes, 1 to 2 seconds in duration, of alternating hypertonia and hypotonia occurred. The electromyogram, however, was normal. The gait appeared normal during the first few steps; then, the left foot exhibited an inward rotation, yet was placed in a normal position. Inward rotation of the left foot did not occur when the patient walked backward. When she struck a match or reached for a small object, the arm was over-extended at the elbow, the humerus was slightly abducted, and the forearm was in extreme supination. The wrist was held in flexion. The phalanges were extended and the fingers bent at the metacarpal joints. The whole movement was executed skillfully and quickly with a peculiar twisting motion which affected the entire arm.

When the patient performed repetitive movements with her hands the flow of motion became more physiologic. Although the over-extension at the elbow and the flexion of the wrist persisted during writing, her handwriting was legible and fluently executed.

The patient related that she first noticed a drawing sensation in the left foot at age 10. The bizarre movements of the hands started at age 24, and the condition remained unchanged ever since. At age 20, she had an episode of blepharospasm lasting several months, which subsided after treatment by an osteopath. She did not feel incapacitated by the motor disturbances.

IV-17: This 23-year-old female was apparently afflicted in a similar way but to a lesser degree than IV-10. We did not have the opportunity of examining her. Her medical records show that, as a child, she "developed a peculiar limping of the left leg." Physical examination at that time revealed "no evidence of paresis or of joint disease. The patient had no hyperkinesia." There has been reportedly very little, if any, further progress of this handicap.

It is interesting to note that IV-10 presents a "paradoxical kinesia," which was first described by Wimmer.[2] Although this is generally considered to be a rare and transitory manifestation of dystonia, it would appear that, in its mild and nonprogressive forms, "paradoxical kinesia" might be a persistent phenomenon. This discrepancy could be resolved in the following way: Paradoxical kinesia is present only during that stage of the disease characterized by action dystonia. As soon as volitional movements become impaired by dystonic hyperkinesias and postures, paradoxical kinesia can no longer occur.

Probably specialized and restricted forms of "action dystonia" or "dystonic dyssynergia" are speech disturbances. Most patients suffering from dystonia musculorum deformans eventually have a peculiar verbal dysrhythmia with slurring and dysarthria. Typically, these patients present explosive verbalizations, rapid involuntary changes of the tempo of speech, and poor pronunciation. All of the full-fledged cases in Family P. included this type of dystonic dysarthria. On the other hand, a number of family members were afflicted with a much

PROBABLE MANIFESTATIONS OF FORMES FRUSTES OF DYSTONIA MUSCULORUM DEFORMANS IN FAMILY P.

		Dyssynergias		*Postural anomalies*			
Code	*Age*	*Dysarthria*	*Dyssynergia of motion*	*Kypho-scoliosis*	*Pes equinovarus*	*Hyperkinesias Blepharospasm*	*Mental retardation (IQ)*
IV-9	38				+		?
IV-10	37	+	+			+	Moderate (57)
IV-14	29	+	+	+		+	Mild (68)
IV-17	23	+	+				?
IV-20	15	+					Mild
IV-21	15	+					Mild
V-4	10	+					Mild
V-5	9	+					Mild
V-7	6	+					Mild
V-11	9						Severe
V-20	2				+		?

less pronounced speech defect manifested by an inability to pronounce certain consonants, such as r, f, and s.

It will be noted from the table that most of the family members in whom dysarthria constituted the only abnormality suggestive of a forme fruste of dystonia musculorum deformans were still under 16. Since the disease may begin as late as the fourth decade of life, it can be anticipated that, in some of these cases, other manifestations of the disease might yet develop.

At least 2 other authors confirm the occurrence of such speech defects in dystonia musculorum deformans. Regensburg[7] reported on a family in which the father and none of the 8 children could pronounce an r, although only 2 of them exhibited classic dystonia musculorum deformans; 5 members of the family had speech disturbances that were much more severe and, in the opinion of Regensburg, typical for dystonia. However, inability to pronounce r is so widely occurring on a cultural basis that it might be suspected that a least some of the 8 children in Regensburg's family acquired their speech defect by learning to imitate their siblings. Nevertheless, von Keyserlingk[8] also stated that difficulties of speech occurring in families afflicted with dystonia should be considered as forme fruste of this hereditary condition. His observations concerned a father and 3 children suffering from classic dystonia, while the father's sister and another child showed only dysarthria.

Postural anomalies and contracture deformities. The diagnostic significance of dystonic postures and contracture deformities rests chiefly upon their combination with dystonic hyperkinesias. In the present family, however, some members exhibited postural anomalies and contracture deformities not associated with dystonic movements.

It will be noted that, of 55 members of 2 consecutive generations, 2—either siblings or first cousins of patients with hereditary dystonia—had *congenital pes equinovarus.* This incidence is approximately 40 times higher than the expected rate for an unselected population. IV-9 is now 38 years old and allegedly has not had any other signs of dystonia. V-20 is now 2 years old. He, too, has no other signs of the disease. Both, however, have 1 parent in whom the diagnosis of dystonia musculorum deformans appears well established.

Increased incidence of congenital pes equinovarus in families with dystonia has not been observed previously.[9] It could be argued that this combination is purely incidental. On the other hand, one should not overlook the relatively high occurrence of pedal malformations in cases of congenital diseases or malformations of the central nervous system. Furthermore, among 185 living fraternal twin siblings of 216 probands with congenital pes equinovarus, Idelberger[10] found 1 case of spastic torticollis. Although this combination might again be fortuitous, both instances together show a correlation between congenital pes equinovarus

and dystonia which seems more than coincidence. In addition, it has long been known that pes equinovarus frequently develops in the course of familial dystonia.[11] Therefore, it appears safe to suspect that congenital clubfoot may represent a forme fruste of hereditary dystonia in selected instances.

A postural anomaly invariably found in those members of Family P. affected with classical dystonia is *kyphoscoliosis*. This is believed to be the result of continuous unilateral spasms of the axial muscles[13] and thus has a pathogenesis similar to that of acquired pes equinovarus. In one patient (IV-14), however, kyphoscoliosis was present without dystonic movements. This man also exhibited a very mild "action dystonia" of his feet, as well as dysarthria. Nevertheless, his chief complaint was blepharospasm, as is described below.

To quote an instance of contracture deformity from the literature, reference is made to Beilin's[11] case D-10. This was the mother of 7 children, 2 of whom had definite hereditary dystonia. A brother, a maternal aunt, and a maternal uncle also had dystonia. D-10, however, is listed as healthy despite the fact that she exhibited a contracture of the left arm which allegedly developed during her adolescence from painful muscle spasms. This suggests that abnormal postures in the absence of overt dystonic hyperkinesias might well be the result of a transient episode of dystonic movements, which, in the cases of the congenital contractures, might even have occurred during fetal life. Obviously, much more study is necessary in order to elucidate these mechanisms.

Hyperkinesias. One of the most characteristic features of dystonia musculorum deformans is hyperkinesia. Although Herz[12] was able to differentiate typical dystonic hyperkinesias from choreic and athetoid movements by cinematography, there is often considerable overlap between these different types of hyperkinesias in one and the same case of dystonia. It is also known that tics and muscular twitchings may occur in hereditary dystonia.[13] Blepharospasm, to our knowledge, thus far has not been described in this condition. Yet IV-10 and IV-14 exhibited this feature in classical fashion, so that it should be included among the hyperkinesias which can be seen in dystonia. IV-14 was first admitted two years ago to a psychiatric institute at the age of 27. The initial diagnosis was conversion reaction and treatment consisted of psychotherapy and hypnosis. However, the blepharospasm has persisted. This represents a contrast to his sister, IV-10, whose blepharospasm disappeared about one year after it onset.

Blepharospasm is occasionally observed in postencephalitic parkinsonism.. It is of particular interest in this connection that, in one of the best described cases of hereditary dystonia, the first case of Schwalbe,[14] the patient presented typical parkinsonian features in the form of pill-rolling movements, rigidity, and masked face many years after the typical signs of dystonia had developed. Maas,[15] who reported this case, explicitly speaks of a parkinsonian state as a late development in the course of dystonia. Similar observations were made by Mendel[6] and by Wechsler and Brock[16] in cases of idiopathic dystonia. If parkinsonian-type symptoms could be accepted as characterizing some cases of hereditary dystonia, both the mother and maternal grandfather of the Lewin siblings, described by Schwalbe,[14] Regensburg,[7] and others, can be considered as having had formes frustes of hereditary dystonia. As described by Regensburg, they both had rhythmic tremors and shaking of the arms aggravated by emotional stress. Again, it appears necessary to point out that much more study is required before the actual significance of those hyperkinesias in cases of hereditary dystonia can be fully understood.

Intellectual impairment. One of the most impressive and provocative observations on Family P. was the high incidence of intellectual deficits. At first, this appeared to be an unrelated family trend because all the members of family P. seen initially by us appeared mentally dull. However, after a more careful evaluation of the family history, it became clear that many siblings of those affected by the disease were of normal and above-normal intelligence and were engaged in successful business ventures or in professions. On the other hand, 6 family members with classic dystonia had IQs ranging from 49 to 77. II-16 and III-12 were already dead at the time of study, and III-13 was not tested but appeared mentally dull to 2 independent examiners.

Although intelligence testing of those patients suggested to have formes frustes was less complete, as can be seen from the table, almost all of them have to be considered as of below-normal intelligence. Only in IV-10 and IV-14 was intelligence testing obtained, and both these patients were classified at the moron level with IQs of 57 and 68, respectively. The identical twins, IV-20 and IV-21, both failed 2 grades in a rural elementary school and, on clinical grounds, can safely be considered of below-average intelligence. The 3 siblings V-4, V-5, and V-7 all proved impossible to maintain in an ordinary elementary school and had to be placed in special classes, where they are receiving individual tutoring because of their intellectual deficiency. This leaves 3 patients with probable formes frustes of dystonia whose intelligence has not been assessed for want of opportunity to examine them directly. These are IV-9 and V-20, both of whom have pes equinovarus, and IV-17, who has a speech defect and locomotional dyssynergia. While in all these cases mental retardation was associated with either full-fledged or abortive dystonia, there is at least 1 relative in the sibship who is suffering from severe mental retardation without any other sign of dystonia. This is V-11, a 9-year-old girl who still might show other features of dystonia.

The close correlation of the various forms of hereditary dystonia with subnormal intellect raises the question of whether intellectual deficiency can be considered as another manifestation of hereditary dystonia. It is noteworthy that a psychologic consultant who interpreted our results felt that the test performance of the patients with dystonia was more characteristic of organic brain damage than of the so-called familial type of mental deficiency. In other words, it seems that there exists a parallel to the organic dementia of Huntington's chorea.

Although most authors state that dystonia does not commonly impair the intellect, Regensburg[7] had noted mental deficiency to be associated with familial dystonia. Yet, in this author's experience, the relationship was much less clear than in our cases. Of the 8 siblings in his series, 3 had intellectual deficits and dystonia, 4 others were considered of normal intelligence but had dystonia, and the last was an imbecile without dystonia. Of course, Regensburg did not base his statements upon intelligence tests but rather on his own clinical judgment. Von Keyserlingk[8] also noted a correlation between dystonia and mental deficiency; however, he does not elaborate on his observations. Kehrer[17] introduced the term "torsiondystonic idiocy" to designate the combination of dystonia with severe mental retardation observed in 3 sisters. The most outspoken proponent of psychologic disturbances as being an integral part of dystonia is Santangelo.[18] He stated explicitly that the hereditary forms of dystonia differ from the acquired ones by an unequivocal disturbance of intelligence found in hereditary dystonia. This agrees so nicely with our findings in Family P. that we consider it possible that the uncomplicated mental deficiency in V-9 may represent a forme fruste of dystonia, or at least an initial symptom of the disease. Of course, this question cannot be answered at this time but shall be kept in abeyance for future investigation.

COMMENTS

The ccurrence of familial cases of formes frustes of idiopathic dystonia raises the question of whether such formes frustes may also exist in a sporadic distribution.

It is believed that the following observation answers this question in the affirmative. The patient was a highly intelligent 27-year-old woman of Jewish extraction whose parents had immigrated from Eastern Russia forty years ago. They could not be examined, yet were allegedly healthy, as were her 3 siblings. At age 15, the patient first noted a drawing sensation in the right foot when she walked. Later, the foot was "pulled" medially, and rotated inward. This disappeared after a few weeks but recurred intermittantly. Within a year, the left foot was similarly affected and the patient had a peculiar shambling gait with shuffling of the feet before placing. However, placing itself appeared normal. This condition has remained stationary for the past twelve years, and no other symptoms have occurred. Despite the grotesque gait, the patient is an avid and skillful dancer and does not at all feel incapacitated. Neurologic examination by one of us (W.Z.) revealed no abnormalities except for a "dystonic muscle tone," that is, an alternating

hyper- and hypotonia upon passive movements of her legs. The patient had 2 complete diagnostic studies by 2 different neurologists who felt that she presented a case of hysteria. For the past five years, the patient has, therefore, undergone first psychoanalysis and later another form of psychotherapy. Her neurologic symptoms have not changed.

Despite the absence of a familial hereditary trait, it is felt that the combination of muscular dyssynergia with dystonic muscle tone, as well as the constancy of the symptoms, suggests the diagnosis of forme fruste of dystonia. The fact that the highest incidence of hereditary dystonia was originally reported among the Jewish population of Eastern Russia[6] might be taken as supportive evidence. The lack of success of psychiatric treatment also seems to favor this interpretation.

DISCUSSION

The only previous report on formes frustes of dystonia found in the literature[19] concerns a patient with a rather classical dystonic syndrome, which, however, ran a remittent, recurrent course. Obviously, the author applied the third definition of formes frustes to his observation. The correctness of this assumption must be seriously questioned because, as already stated by Ziehen,[20] dystonia musculorum deformans characteristically becomes arrested after having taken a progressive course for a number of years. Furthermore, it is doubtful whether Brunschweiler's[19] case is actually an instance of idiopathic dystonia or just one of the symptomatic forms.

On the other hand, the observations reported here seem to indicate that at least one possible mechanism leading to a forme fruste of dystonia musculorum deformans is a premature arrest of the disease. This contention is suggested by the fact that "action dystonia" and muscle spasms leading to abnormal posture and contracture deformities, suggested by this report as constituting typical manifestations of formes frustes, are at the same time considered to be the initial symptoms of dystonia musculorum deformans. For example, Marrotta[21] reported on a patient who suffered from painful muscle spasms for two years before showing typical signs of dystonia. It is not difficult to recognize here the similarity with Beilin's[11] case D-10 and also to a certain extent with our observations of blepharospasm and of contracture deformities and postural abnormalities. Furthermore, Mendel[22] considered the appearance of dyssynergias as typical initial signs of the disease. Thus, it can be postulated that our subjects IV-10 and 17, as well as others, never progressed beyond this stage. Whether this argument also applies to those subjects with mild dysarthria must await further study. Applying the theory of Gunther and Penrose[1] to this hypothesis, one would have to assume two different genes being responsible for idopathic dystonia: one for the phenotypical manifestations and another for the progression.

Considerable doubt exists as to the significance of mental deficiency alone as a possible forme fruste. If this condition were the expression of the pathogenic gene, one would have to expect cases of dystonia among the offspring of the mentally deficient. This expectation is met only by the family of Santangelo,[19] in which a mother of "poor" intelligence gave birth to 3 children with classic dystonia. Certainly, this scanty evidence is not sufficient to consider mental deficiency a well-documented forme fruste of dystonia, especially if one considers it likely that patients afflicted with dystonia might often find only marriage partners with subnormal intelligence.

The importance of properly recognizing formes frustes of dystonia musculorum deformans is twofold. In the first place, the correct diagnosis will eliminate unnecessary treatment and allow for a more realistic and accurate prognostication. Equally important is the consideration that patients with formes frustes can be carriers of the pathogenic gene, as exemplified by our subject VI-10. Thus, from the aspect of eugenics, the formes frustes of idiopathic dystonia deserve much more attention than they have been afforded hitherto. Yet, it should not be overlooked that, owing to the rarity of the disease and the limited number of cases available for study, the conclusions reached in this study are both preliminary and incomplete.

SUMMARY

Attention is directed to the formes frustes of dystonia musculorum deformans as found in 4 generations of 1 family with this genetic dis-

order. These persons lack the typical dystonic movements and postures. Their manifestations are chiefly dyssynergias, hyperkinesias not commonly related to dystonia, postural abnormalities and contracture deformities not associated with dystonic hyperkinesias, and, possibly, also mental deficiency. It is suggested that, at least in some instances, the formes frustes may be prematurely arrested cases of dystonia. The importance of the recognition of formes frustes as regards treatment, prognosis, and eugenic implications is stressed.

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Neurologic effects of tryptophan in patients receiving a monoamine oxidase inhibitor

John A. Oates, M.D., and Albert Sjoerdsma, M.D., Ph.D.

UNDER ORDINARY CIRCUMSTANCES, dietary amino acids are not considered to be pharmacologically active, After inhibition of the enzyme monoamine oxidase, however, tryptophan becomes an active agent capable of altering central nervous system functions. This phenomenon was discovered during biochemical studies on the formation of tryptamine from tryptophan in man.[1] In the course of these investigations, we had observed no untoward effects from the oral administration of 20 to 50 mg. per kilogram of this amino acid in many patients with a variety of disorders. However, when similar doses of tryptophan were administered to patients undergoing treatment with a potent inhibitor of monoamine oxidase (MAO), definite neurologic alterations occurred. The present report describes these effects in 7 patients and indicates their relationship to alterations in the metabolism of tryptamine and 5-hydroxytryptamine (serotonin).

MATERIALS AND METHODS

The subjects were 7 hospitalized patients, 4 females and 3 males, ranging in age from 18 to 53. All had essential hypertension which in 1 case had been complicated by 2 cerebrovascular accidents with residual left hemiparesis. The other patients had no neurologic abnormalities.

Single doses of L-tryptophan (20 to 50 mg. per kilogram) were administered orally before breakfast, with approximately 200 gm. of apple sauce as a vehicle. Monoamine oxidase inhibition was achieved by the administration of 25 mg. of β-phenylisopropyl hydrazine (Catron) at 6 A.M. daily for at least four days. Measurements of urinary tryptamine[2] indicated the achievement of marked enzyme inhibition that had reached a "plateau" in this time. The dose of tryptophan in each patient had been previously shown to produce no detectable effects on one or more occasions in control studies.

RESULTS

The observations will be described in relationship to the dose of tryptophan and time of its administration. The effects observed occurred in the absence of any significant change in blood pressure or heart rate.

Dose: 20 mg. per kilogram (3 cases)

1. A 45-year-old white female. Within two hours, the patient felt somewhat drowsy and, on attempting to walk felt "drunk." Aside from a slightly unsteady gait, no objective neurologic changes were noted. The alterations disappeared within ten hours.

2. A 39-year-old colored female with preexistent left hemiparesis and associated hyperreflexia, resistance to passive stretch, and Babinski sign. After tryptophan, a sensation of "dizziness" occurred on standing (without blood pressure change) as well as easily induced left ankle clonus and clonic tremors in both the left arm and leg. No changes appeared on the right side. These effects disappeared within twelve hours.

3. A 53-year-old white female. A transitory and mild incoordination of gait was observed. In addition, she experienced a "chilly" sensation that was most marked in the feet and legs and complained of slight nausea.

Dose: 30 mg. per kilogram (2 cases)

1. An 18-year-old white female, wife of a ministerial student. Within two hours after tryptophan, she stated that she felt "woozy" and "lightheaded;" this was more marked on standing. When trying to walk she felt quite unsteady and at times requested assistance. While lying down, she felt as if she were "floating." In addition, she had disturbing "funny, hot feelings" on her feet, legs,

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and chest, sensations that were later accompanied by numbness and tingling in the same areas. She became very restless, and her speech became slower and higher pitched than usual. The manner in which she spoke was remarkably uninhibited in comparison with that noted before. This, in combination with a staggering gait, prompted observers to liken her status to ordinary drunkenness.

On examination seven hours after tryptophan administration, the Romberg was slightly positive. The pupils were moderately dilated but reacted normally. Also noted were mild gross tremor of the tongue and a quite hyperreactive jaw jerk which, when elicited, would sometimes result in clonus. Corneal reflexes were slow but present. The sensory examination seemed normal except that she gave conflicting answers to pain and light touch stimuli applied to the lower extremities. By this juncture, she had an attitude of jovial irresponsibility, and the validity of any sensory findings are doubtful. In the upper extremities, there was no resistance to passive stretch, coordination was minimally impaired, and deep tendon reflexes were normal. However, the lower extremities presented a quite different picture, with marked resistance to passive stretch accompanied by hyperreflexia and easily induced sustained clonus at both the knee and ankle. At times, there would be uncontrolled trembling of the legs. Attempts to elicit a Babinski sign only provoked withdrawal. By the end of twelve hours, the various alterations had subsided.

2. *A 52-year-old colored male.* During treatment with the monoamine oxidase inhibitor, he became distinctly more lively and outgoing, the only patient in the series who showed any obvious central changes on the inhibitor alone. However, no other neurologic changes occurred until administration of tryptophan. About two hours after ingestion of the amino acid, he stated that he felt as if he had had a drink of whisky, describing himself as feeling "wildish." All observers concurred that he seemed inebriated as he walked about the unit in a somewhat inappropriate expansive mood, slapping people on their backs and talking loudly. He suspected that this tryptophan was not the same as he received before beginning the inhibitor and was quite happy about it all.

At this time, gait was not appreciably impaired and the Romberg sign was absent. The biceps, triceps, radial, patellar, and Achilles tendon reflexes were hyperactive, but the jaw jerk was normal. Sustained clonus could be induced in the left quadriceps. The Hoffman reflexes were positive. Planter response was normal except for marked withdrawal. Within twenty-four hours, his status had returned to that seen before tryptophan.

Dose: 50 mg. per kilogram (2 cases)

1. *A 28-year-old colored male.* After about ninety minutes, he stated that he felt as if he were "on a cheap drunk," which seemed to be a pleasant sensation, defined by him as "just rosy." The sensation of intoxication increased, accompanied by mild dysarthria, staggering gait, and a very silly affect. Mild ptosis developed, accompanied by drowsiness. The gait appeared quite incoordinated, though the Romberg was only slightly positive. The jaw jerk was hyperreactive and was followed by sustained clonus of the masseters. At times, there was spontaneous jaw clonus and his teeth would chatter as if he were having a chill. Upper extremity coordination seemed intact, but coordination of the legs was moderately impaired. No tremor of the outstretched hands was seen. The biceps and triceps tendon reflexes were slightly increased. The patellar and Achilles reflexes were very hyperactive, however, and ankle clonus could be induced. Plantar responses were normal. After eight hours, his speech had cleared and coordination of gait returned, along with subsidence of the feeling of intoxication. Only hyperreflexia of the lower extremities and jaw clonus persisted, the latter still occurring spontaneously at times and causing the patient to be concerned. After twenty-four hours, all neurologic changes had disappeared.

2. *A 37-year-old white male.* After three hours, he became drowsy and actually fell asleep briefly. Nothing else occurred to suggest altered mental status. Other changes appeared, however, including profuse diaphoresis and occasional spontaneous jerking movements of the legs. Gait was unimpaired, and the only other positive findings were hyperactive patellar and Achilles reflexes and sustained ankle clonus. These changes persisted for about eight hours.

DISCUSSION

The administration of tryptophan during MAO inhibition produced neurologic effects in each of the 7 patients studied. The most striking alterations were changes in mental status resembling ethanolic intoxication, which occurred in 3 of the patients. In addition to ataxia, central effects including euphoria, release from inhibitions, inappropriate or silly affect, dysarthria, and the characteristic countenance were sufficient to impress observers with the similarity to ordinary drunkenness. Drowsiness was observed in these patients as well as those who had no ethanol-like central effects. This inclination to sleep is notably dissimilar to the usual psychic energizing effects reported with the use of MAO inhibitors alone.

All patients receiving tryptophan in doses of 30 mg. per kilogram or greater during MAO inhibition exhibited hyperreflexia in the lower extremities accompanied by ankle clonus. In no case was there a comparable degree of hyper-

reflexia in the upper extremities, though clonus of masseters was observed in 2 cases. Since there was no instance of extensor plantar reflexes, the peripheral manifestations seem to represent hyperreflexia on some basis other than upper motor neuron deficit.

The occurrence of these phenomena only when tryptophan was given during inhibition of amine metabolism by a MAO inhibitor suggests that the central actions are mediated through one or more of the amine metabolites of the amino acid. Tryptamine and serotonin are two amines known to be formed from tryptophan in man. Tryptamine arises directly by decarboxylation of tryptophan, whereas hydroxylation of tryptophan precedes decarboxylation in the formation of serotonin. L-aromatic amino acid decarboxylase, the enzyme responsible for both of these decarboxylations, is present in the central nervous system. After the present observations in man, it was shown in rats that administration of tryptophan increased the levels of both tryptamine and serotonin in the brain, the increase being most marked if the animals were pretreated with a MAO inhibitor.[3,4] Indications of central effects were also observed in the latter circumstance. The increased level of brain serotonin after administration of 5-hydroxytryptophan is known to be accompanied by central effects which vary according to the species.[5] Tryptamine will also produce central neurologic effects in animals, and the potentiation of tryptamine convulsions in rats has actually been used by Tedeschi, Tedeschi, and Fellows[6] as a means of detecting the MAO inhibition produced by various drugs in vivo. In the subjects of the present study, the combination of tryptophan administration with MAO inhibition resulted in increases in urinary tryptamine to levels as high as 25 times control. Increases in the urinary excretion of the serotonin metabolite, 5-hydroxyindoleacetic acid, have been demonstrated after oral administration of large doses of tryptophan in man.[7] Thus, it is reasonable to conclude that, during MAO inhibition, the concentrations of tryptamine and serotonin in the human nervous system may be elevated by tryptophan adminstration. Although further investigation is required before either tryptamine or serotonin may be implicated individually in the observed neurologic phenomena, it seems likely that one or both of these amines is involved.

The doses of tryptophan which produced neurologic effects were only 1.5 to 3 times the usual daily dietary intake of this amino acid. This raises the question of whether variations in the dietary intake of this and other amino acids may modify the clinical effects and side effects seen during therapeutic use of MAO inhibitors. It has been reported that combined therapy with tryptophan and iproniazid has more therapeutic effect on psychotic patients than iproniazid alone.[8] Although our observations do not have obvious therapeutic implications, they do provide conclusive evidence that a dietary amino acid may influence the action of MAO inhibitors.

SUMMARY

The oral administration of 20 to 50 mg. of L-tryptophan per kilogram to 7 patients during therapy with a monoamine oxidase inhibitor produced neurologic effects including ethanol-like intoxication, drowsiness, hyperreflexia, and clonus. The possible mediation of these effects by tryptamine and serotonin and implications in the clinical use of MAO inhibitors are discussed.

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A possible explanation of the mechanism of ophthalmoplegic migraine

James P. Walsh, M.D., and Desmond S. O'Doherty, M.D.

SINCE FIRST reported by Gubler in 1860,[1] ophthalmoplegic migraine has been the subject of controversy, particularly regarding its designation as a disease entity. Since both clinical cases and autopsy material are scarce, the definitive diagnosis of ophthalmoplegic migraine has depended on [1] the clinical picture and [2] the elimination of other causes by arteriography or surgical exploration.

That ocular palsies occur during the course of classical migraine is well known.[2] These are not common and most frequently involve the third nerve. Total ophthalmoplegia is a rare finding.

In the absence of other diseases, it is probable that headache and ophthalmoplegia are caused by the same mechanism. The most reasonable explanation is that the third, fourth, and sixth nerves are affected in their peripheral course, possibly through pressure from an edematous internal carotid artery. Anatomically, such pressure could most readily occur in the cavernous sinus. The following factors favor this location:

- *The clinical picture.* Many patients with a typical migraine syndrome have, after many years, developed a demonstrable extraocular paralysis that cleared between attacks.[3]
- *Pupillary involvement.* When total ophthalmoplegia occurs, the pupil may be affected. This indicates involvement of the third nerve in its peripheral course.
- *Anatomic relationship.* The fourth nerve, when involved, is ipsilateral to the third and sixth nerves. The first division of the fifth nerve may at times be affected (Case 1), again indicating a peripheral location.

The combination of ophthalmoplegia and a migraine-type headache can result from a variety of causes, such as tumors of the third and fifth nerves, aneurysms with or without rupture, vascular anomalies, and intracerebral temporal lobe hemorrhage. The situation, therefore, deserves clarification. Such clarification must begin with establishment of criteria for diagnosis. The criteria which we believe essential are:

1] A history of typical migraine headache, that is, a severe throbbing headache usually unilateral, but occasionally bilateral or alternating. It is typically of the crescendo type and may last several hours or days.

2] Ophthalmoplegia. This may include one or more nerves and may involve one side or may alternate sides with attacks. Extraocular muscle paralysis may occur with the first attack or, rarely, precede it. Usually, however, paralysis appears subsequent to an established migraine pattern.

3] Exclusion of other causes by arteriography, surgical exploration, or autopsy. Certainly one may suspect ophthalmoplegic migraine in any case of intermittent ocular palsy with headache, but the clinical picture alone is not enough for a definitive diagnosis. Therefore, arteriography is the minimum additional requirement for diagnosis.

Approximately 200 cases have been recorded as ophthalmoplegic migraine. Unfortunately, many of these are not clear-cut and must be definitely excluded. For example, at least 7 patients did not have histories of headaches at all.[4] In 3 cases,[5,6] only one attack was described without a previous history of headache. Other cases demonstrated a definite disease that was capable of producing the clinical picture.

We have selected from the literature the

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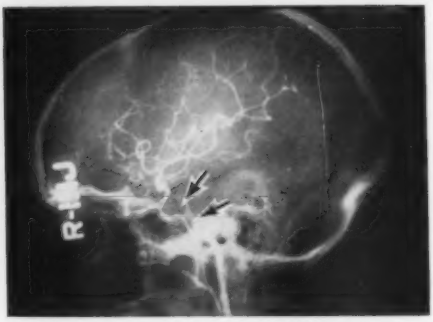

Fig. 1 (Case 1, first admission). Right carotid arteriogram showing narrowing of distal portion of the artery

histories of those patients who had autopsy, arteriography, or surgical exploration.

Autopsy material is scarce despite the number of cases of this syndrome in the literature. We were able to find only 8 cases with postmortem findings. Of these, only 1 can be definitely classified as uncomplicated ophthalmoplegic migraine. Of those rejected, 2 had tuberculosis involving the third nerve,[7,8] 1 had meningitis,[1] 2 had tumors of the third nerve,[9,10] 1 had metastatic cancer,[3] and 1 had a ruptured aneurysm.[11]

The second case of Alpers and Yaskin is the only convincing autopsied case.[12] This patient fulfilled all 3 criteria: she had migraine attacks free from accompanying ocular paralyses, subsequent episodes associated with paralysis, and no evidence, either clinically or by autopsy, of any other organic cause for the symptom complex.

Arteriography has supplied a useful tool for investigation of this condition. It is helpful in ruling out some of the other conditions likely to cause ophthalmoplegia and, as in the present study, gives a picture of the vascular conditions at the time of the ophthalmoplegia.

A group of cases[12-15] in the literature describe classical migraine associated with diplopia and often with such signs of third nerve palsy as ptosis or extraocular muscle involvement. Arteriograms in all these cases were reported as normal.

While few recorded cases present a convincing picture of classic ophthalmoplegic migraine, some are incontrovertible. In the early literature, the cases of Townsend,[16] Finlay,[17] Nason,[18] Saundby,[19] Carpenter,[20] Veasey,[21] and others have clinical pictures that are clear enough to suggest a probable diagnosis of ophthalmoplegic migraine, despite the lack of more definitive tests. The same is true for the case histories of Walsh[22] and Ford[15] in the more recent literature.

In 3 cases seen by us, the above criteria were fulfilled. These are presented below.

CASE REPORTS

Case 1 (P.M.). A 23-year-old female had a chief complaint of inability to open her left eye during the preceding eight hours.

She had apparently been well throughout her entire life except for severe headaches that occurred several days before the onset of her menstrual periods. Frequently these were associated with nausea and vomiting. Unilateral in location, they at times occurred on one side, at times on the other.

Five months before her first admission, she had a two-week bout of severe headaches. She was unable to open her right eye and had some vague numbness and tingling in her right arm and leg. She had had complete opthalmoplegia of the right eye involving the third, fourth, and sixth cranial nerves and the first division of the fifth cranial nerve. When she was admitted to a local hospital, a lumbar puncture was normal. Bilateral carotid arteriography showed a single abnormality—narrowing of the intracranial portion of the right carotid artery (Fig. 1).

The patient underwent an exploratory craniotomy on the right side which revealed nothing abnormal. In the course of a two-month period, she regained complete function of her right eye.

Two weeks before her second admission, the patient noticed the onset of a severe left occipital headache associated with nausea and vomiting. Eight hours before admission, she was unable to open her left eye and had retroorbital pain on the left side.

Physical examination. The left pupil was fixed in midposition and did not react to light or accommodation. There was complete ptosis (Fig. 2), and the eye could not be moved in any direction. Sensation was decreased over the first division of the left fifth cranial nerve, but the remainder of the cranial nerves were normal. The peripheral nervous system was entirely intact.

Family history. All aunts and uncles on the maternal side of the family had, since childhood, experienced severe headaches associated with nausea and vomiting. Some apparently had an aura with these headaches.

All laboratory findings, including lumbar puncture, were normal.

Bilateral carotid arteriography was performed. At this time, the cervical and intracranial portion of the left carotid artery was narrowed and the right carotid was normal (Fig. 3).

Case 2 (J.D.). A 35-year-old Negro male had a history of dull right temporal headaches beginning at the age of 19. They occurred every three to six months, lasted two full days, and were followed by diplopia that lasted for one month. The headaches became more severe and just before admission were accompanied by nausea, dizziness, and radiation of pain to the right postauricular area. Physical examination was negative except for diplopia which was the result of a weakness of the left superior rectus muscle. A left carotid arteriogram showed no gross abnormalities, but there was a suggestion of constriction of the internal carotid artery intracranially (Fig. 4).

Case 3. This 15-year-old patient had 3 hospital admissions. The first occurred at the age of 12, when she had diplopia of two days' duration accompanied by headache. She had had bilateral frontal headaches for two or three months prior to her admission. Physical examination was normal except for questionable strabismus. Twice during hospitalization, Prostigmin was given with good response. She was discharged with a diagnosis of probable myasthenia gravis.

Nine months later she was hospitalized for further evaluation. Despite oral Prostigmin medication, the patient had 4 episodes of diplopia. Physical examination was again normal. The laboratory workup was normal except for occasional brief runs of 6-per-second square waves on the electroencephalogram.

Two years later, she was readmitted with an interim history of 2 mild episodes and 1 severe episode of a unilateral throbbing headache followed by diplopia and "crossed eyes." On the day before admission, the patient was seen in the clinic and internal strabismus was noted. Prostigmin afforded no relief. Her symptoms disappeared during the next two days. Light hurt her eyes, so she preferred to lie in a dark room. Carotid and vertebral arteriograms were normal.

Fig. 2 (Case 1, second admission). Showing complete ptosis as part of complete left ophthalmoplegia

DISCUSSION

The etiology of the ophthalmoplegic migraine syndrome is as obscure as the etiology

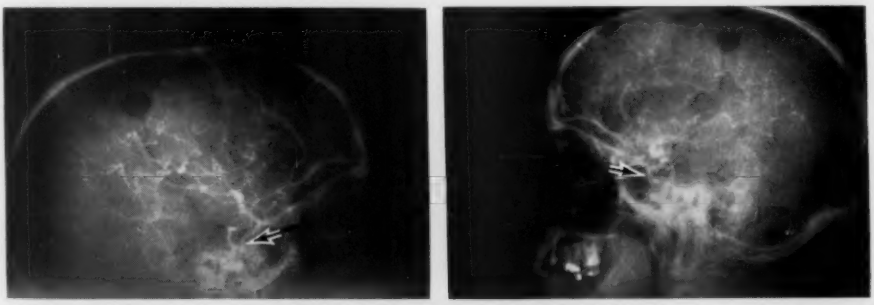

Fig. 3 (Case 1, second admission). *[Left]* Left carotid arteriogram showing narrowing of intracranial portion of artery. *[Right]* carotid arteriogram of same patient; artery of normal size

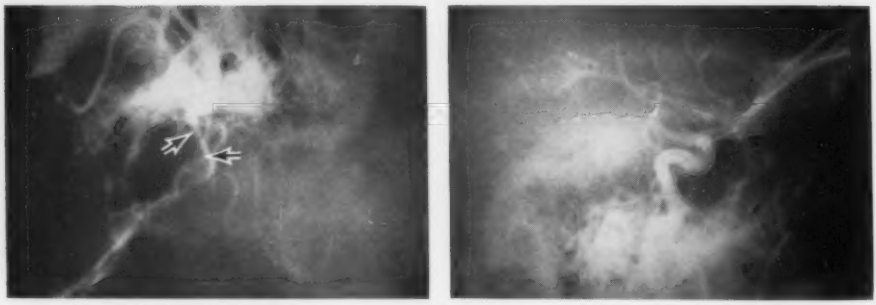

Fig. 4 (Case 2). *[Left]* Left carotid arteriogram showing a constriction of distal portion of the artery. *[Right]* Right carotid arteriogram showing normal vessel

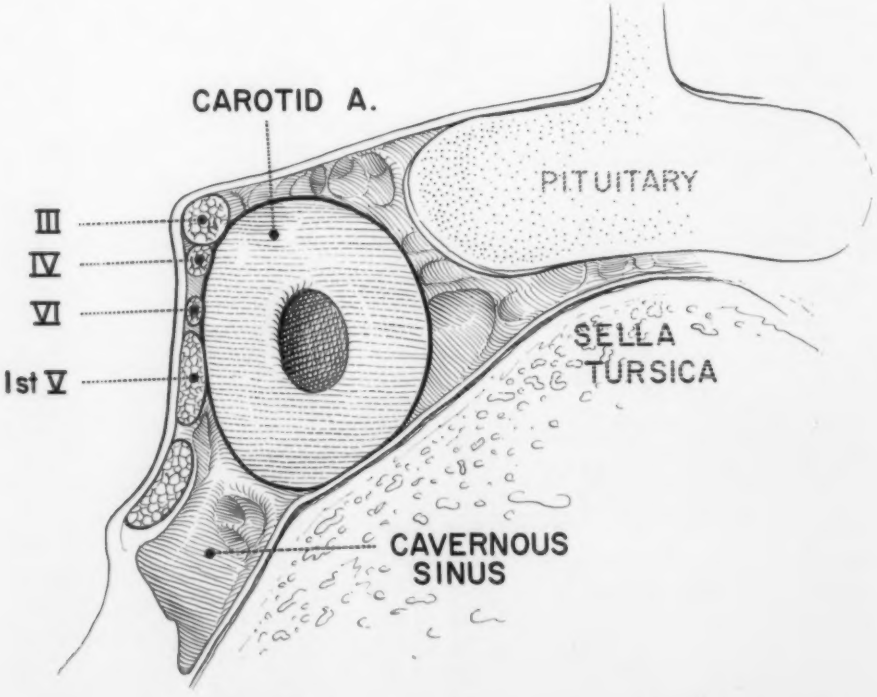

Fig. 5. Diagram showing possible mechanism of ophthalmoplegias — a process involving either pressure on the nerves or ischemia of the nerves caused by changes in the internal carotid artery

of migraine itself. However, it is probable that a mechanical factor is involved. It is usually assumed that the end stage of migraine is caused by, or is associated with, edema of the intracranial vessels. These edematous arteries can, in turn, exert pressure on neighboring nerves (Fig. 5).

Several factors justify the theory of periodic pressure by edematous arteries on the involved nerves:[23]

1] The ophthalmoplegia is always a peripheral-type paralysis. The character of the symptoms clearly indicates that the nerve or nerves are involved in their extracerebral course.

2] A vascular cause is suggested by the sudden onset and gradual subsidence of the episodes.

3] The process is usually transient, although a permanent paresis may sometimes occur.

4] Instances of involvement of the third, fourth, or sixth cranial nerve or combinations of the three do occur.

5] In some patients, the use of vasoconstrictor drugs has relieved the ophthalmoplegia.[24]

6] Four cases with arteriograms (case of Alpers and Yaskin,[12] the case of Verbrugghen,[13] and 2 cases reported here) demonstrate an interesting finding—a narrowing of the distal portions of the carotid artery. This may represent an edematous swollen vessel as the end result of the factors involved in migraine—a result that occurs regardless of what the basic etiology of these factors may be (Fig. 5).

Goltman[25] demonstrated that volume changes within the cranium may occur as an effect of dilation of the cranial arteries and thickening of these vessel walls. He was able to observe the swelling and regression of cranial contents through a defect in the frontal bone. During the late stages of migraine, an increase in swelling of the cerebrum was evident.

By studies before, during, and after an attack of migraine, Naffziger[26] demonstrated a shift of a calcified pineal gland. A definite displacement away from the side of the headache was shown.

These studies indicate generalized cerebral edema, which might explain the oculomotor nerve paralyses on the basis of uncal herniation or involvement of the abducens nerve but would not account for involvement of the trochlear nerve or involvement of all 3 nerves unilaterally.

CONCLUSIONS

Findings in our cases lead us to conclude that the basic pathophysiology of simple migraine and ophthalmoplegic migraine is the same, namely, a 2-phase vascular process. The more severe phase (swollen edematous arteries) is the immediate cause of the ophthalmoplegia, either by direct pressure on the nerves or by the edema interfering with the vasa nervorum to these nerves in their peripheral course. This contention is supported by the fact that [1] in a majority of cases, the paralyses occur after many years of simple migraine and [2] in each individual attack, paralysis occurs several hours or days after the headache phase.

The narrowing noted in the arteriograms is most likely the result of swelling of the artery.

SUMMARY

1] The problem of ophthalmoplegic migraine is examined and criteria for diagnosis are suggested. Three cases are added to those which fulfill the criteria.

2] Arteriography occasionally shows a narrowing of the internal carotid artery in the cavernous sinus. We conclude that this narrowing is the result of edema of the arterial wall.

3] The mechanism of the ophthalmoplegia is probably the pressure on, and/or ischemia of, the third, fourth, and sixth nerves in their cavernous portions.

The authors are indebted to Dr. Alfred Luessenhop for permission to use his arteriogram in Case 1.

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Medical treatment of intracranial aneurysm

An analysis of 15 cases

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THIS is a report of a medical method of treating acute ruptured aneurysm, the results of which appear to be better than the results of surgical methods; 15 cases of subarachnoid hemorrhage with proved aneurysm were treated by the medical method of induced hypotension.[1]

CASE MATERIAL

In considering case material, it is important to remember that, with other methods (surgical), there are many kinds of selection used. In fact, there are at least 8 ways by which surgeons restrict their cases.[2,3] Operation is withheld because of [1] age—the patient must not be more than 50 to 55 years old—[2] complicating medical illnesses, such as coronary insufficiency, hypertensive disease, and history and/or laboratory evidence of bleeding tendency, [3] absence of demonstrable cross circulation, [4] reaction to carotid compression, [5] inaccessibility of aneurysm, [6] presence of multiple aneurysms, and, especially, [7] *recency of bleeding*—relatively few operations are performed within twenty-four hours of a hemorrhage. All of the above 7 restrictions affect surgical methods of treatment. In contrast, an eighth restriction in surgical series is the only one applied with the medical method, that is, the patient must be able to communicate at the time treatment is begun. This is necessary because the hypotensive method depends on a reversible alteration in the communicated part of the neurologic examination.[4] Many more cases can be treated by this medical method than by surgical methods. It is pointed out that a history of coma at the start of the illness does not rule out this method of treatment. Many patients recover from an initially unresponsive state and can be treated before they have a fatal recurrence. In fact, of the 15 patients presented in this report, 11 had had at least 1 episode of coma during the illness.

LOCATION OF THE ANEURYSM

There were 9 aneurysms of the anterior communicating artery, 3 of the internal carotid—posterior communicating artery system, 2 of the anterior cerebral artery, and 4 of the middle cerebral artery. There were 3 cases of multiple aneurysm.

ANTECEDENT MEDICAL ILLNESSES

Hypertension was present in 8 cases, coronary insufficiency in 1, history and/or laboratory evidence of bleeding tendency in 2, and evidence of poor collateral circulation in 3. One patient had 7 other illnesses as well as poor cross-circulation.

MEDICAL METHOD

The detailed management by induced hypotension has been discussed elsewhere.[4] In brief, the patient's blood pressure is regulated by drugs primarily on the basis of many neurologic examinations. Apparatus used includes a tilt table, and, more recently, an electronic blood pressure follower* has been added. Drugs used are pentolinium, reserpine, chlorothiazide, hydrochlorothiazide, hydralazine, and syrosingopine.† They are continued indefinitely.

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*The blood pressure follower has been kindly loaned by Dr. Andrew J. Presto of Winston Electronics, Ltd.

†Reserpine (Serpasil), syrosingopine (Singoserp), hydrochlorothiazide (Esidrix), and hydralazine (Apresoline) were supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J. Chlorothiazide (Diuril) and hydrochlorothiazide (HydroDiuril) were supplied by Merck, Sharpe and Dohme, Inc., Philadelphia.

	Interval between onset of original hemorrhage and treatment	Age	Sex	Location IC*	ACC†	AC‡	MC§	Multiple aneurysms	Loss of consciousness	Remarks	Results	Length of follow-up
	0 to 24 hours									Known hypertension for 8 years; protracted mouth bleeding 4 times after tooth extraction; recurrent subarachnoid hemorrhage in hospital;	Well; fully active	2 years, 8 months
M.M.	Less than 9 hours	51	F		X				Yes	treated immediately; recovered		
M.S.	19 hours	29	F	X					No	1 year after discharge, hypotensive medication was altered (elsewhere). This was followed by right third nerve paralysis. Medication resumed. Recovery	Well; fully active	2 years, 8 months
E.C.	24 hours	32	F		X				Yes	Known hypertension for 2 years; recurrent subarachnoid hemorrhage in hospital; treated immediately; recovered	Well; fully active	3½ years
	25 to 48 hours									? hypertension. Multiple subarachnoid hemorrhages in hospital; each treated immediately with recovery from each hemorrhagic episode, but died 3½ months after last hemorrhage;	Dead	
S.W.	29 hours	58	F		X				Yes	anomalous posterior communicating artery		
C.H.	36 hours	44	F	X	X			X	Yes	Before treatment, patient had 2 subarachnoid hemorrhages, 17 days apart, with residual severe visual damage secondary to vitreous hemorrhages (bilateral); no hemorrhage since treatment	Improving	Recently discharged (April 27, 1960)
C.J.	40 hours	57	M		X				Yes	Known hypertension for 1 year; coronary insufficiency for 1½ years; bleeding tendency (history) plus abnormal prothrombin time (twice)	Well; as active as prehemorrhage	1 year
	3 to 7 days									Known hypertension for 25 years; severe psychiatric illness for 13 years with electroshock therapy twice then marsilid; hepatitis, then subarachnoid hemorrhage, then recurrent	Same as before hemorrhage except for slight dysphasia secondary to hemorrhage	1½ years
F.T.	5 days	68	F				X		Yes	subarachnoid hemorrhage		
S.D.	7 days	48	F				X	X	No	2 aneurysms of middle cerebral artery	Well; fully active	1½ years
	8 to 14 days									Medical history: hypertension, rheumatic fever, chorea, colitis, phlebitis, bronchitis, arthritis. Angiography: besides aneurysm, evidence of poor cross-circulation (anomalously narrow arterial segment)	Well; increasing activity now	10 months
E.S.	14 days	40	F		X				No			

15 to 21 days											
C.S.	15 days	60	F		X			Yes	Angiography; besides aneurysm, evidence of poor cross-circulation (anomalously narrow arterial segment); Discharged well; probable recurrent hemorrhage at home	Dead	
R.M.	17 days	56	M		X			Yes	Recurrent hemorrhage in hospital; treated immediately; recovered; discharged; probable recurrent hemorrhage at home	Dead	
22 to 62 days											
										Moderate aphasia before treatment; slight improvement since then	4 years, 3 months
F.B.	35 days	51	F		X	X	X	Yes	Known hypertension for several years; multiple aneurysms		
B.C.	37 days	62	F	X				Yes	First patient treated by this method. Angiography repeated 3 years later—unchanged, but patient continues to be completely well	Well; fully active	4 years, 3 months
C.T.	About 42 to 56 days, perhaps sooner	65	F			X		No	Bloody, xanthochromic cerebrospinal fluid on admission but symptoms (headache, etc.) had begun few weeks before admission. On admission, "terrific headaches" and left homonomous field defect	No headaches now. Vision slowly improving	5 months
R.P.	62 days	49	F			X		Yes	Known hypertension for several years	Well; fully active	1 year, 1 month

*Internal carotid
†Anterior communicating
‡Anterior cerebral
§Middle cerebral

CASE REPORTS

To illustrate the wide applicability of this method even under difficult conditions, the following cases are outlined. A 57-year-old man was admitted to the hospital because of sudden loss of consciousness. Grossly bloody cerebrospinal fluid was found, and angiography demonstrated a saccular aneurysm of the anterior communicating artery (Fig. 1). The past medical history included evidence of coronary insufficiency, of one and one-half years' duration and hypertension of one year's duration. In addition, there was a history of bleeding excssively when he cut himself shaving and 2 prothrombin time determinations were abnormal. Within twenty-four hours of onset of symptoms of hemorrhage, hypotensive therapy was begun. The patient recovered completely.

Another patient's angiogram is shown in Figure 2. Important features in her case were her age (51), unusually rapid start of treatment (less than nine hours from onset of symptoms of hemorrhage), loss of consciousness at onset of the illness, location of the aneurysm at the anterior communicating artery, and a past medical history that included hypertension for eight years and 4 episodes of protracted bleeding from the mouth after a dental procedure. She also had a recurrent subarachnoid hemorrhage in the hospital. She recovered completely. It is now more than two and one-half years since her hemorrhage. Figure 3 shows an aneurysm in a patient who was 65 years old at the time of hemorrhage. She recovered and has recently been discharged.

RESULTS

Of 15 patients treated, 12 survived and 3 died. In evaluating these results, it is again noted that, in surgical series, the age of 50 to 55 years is commonly taken as the upper limit for operability. Yet, operations even on patients less than 55 years of age carry a significant mortality as well as morbidity. In contrast, in this medical series, there were no deaths in the 8 patients less than 55 years of age. Among the remaining 7 patients, who were all more than 55 years of age, there were 3 deaths, patients aged 60, 56, and 60, respectively; 1 of the 3 who died also had evidence of poor cross circulation of the anterior half of the circle of Willis, another had a thread-like

Fig. 1. *(Case 1)* Angiogram showing aneurysm of anterior communicating artery. Patient was treated and recovered.

Fig. 2. *(Case 2)* Angiogram showing aneurysm of anterior communicating artery. Patient was treated and recovered.

posterior communicating artery,[5] and all 3 had had aneurysms of the anterior communicating artery. Of the 3 deaths, 2 occurred after the patients had recovered (under treatment) from their initial hemorrhages and had been discharged from the hospital. The third death was that of a patient who had multiple hemorrhagic episodes. In the last instance, three months after recovery from the last hemorrhage, the drugs were reduced and then stopped entirely but spontaneous hypotension with hypernatremia occurred, followed by death. At autopsy, the aneurysm was found embedded in the orbital surface of the brain, causing a bilateral concave depression of the brain tissue with residua of previous hemorrhage adjacent to it. The exact mechanism of the spontaneous hypernatremia and hypotension long after discontinuance of drugs is not certain. The embedded aneurysm with its multiple episodes of hemorrhage had exerted pressure upon a region of the brain which experimentally[6] has been shown to be important in regulation of systemic blood pressure.

It is noteworthy that the 4 survivors in the older age group are now 58, 65, 66, and 70 years old, respectively, and continue to take hypotensive medications without difficulty.

The 3 patients who have multiple aneurysms are all alive. Patients with complicating antecedent medical illnesses are alive. A patient with evidence of poor cross circulation is still alive. The 3 patients treated within twenty-four hours of the original onset of symptoms are all alive. Of the 12 survivors, 7 are already considered to show excellent results, 3 more are steadily improving (2 were discharged recently), and the remaining 2 have made slight improvement in their posthemorrhage dysphasia and are fully ambulatory.

COMMENT

The only deaths in this medical series occurred in patients who would probably have been refused surgery because of age, inadequate cross circulation, poor surgical location, and the like. On the other hand, there are patients in this series who have done extremely

well but who also would have been refused surgery for a variety of reasons. This much larger group of survivors includes 6 with aneurysm of the anterior communicating artery. No patients with aneurysms in other sites died.

The most important use of this medical treatment is during the earliest stage of hemorrhage — the first twenty-four to forty-eight hours. Thus, there were 12 hemorrhagic episodes proved by lumbar puncture in which hypotensive therapy was applied *as an emergency measure and without a single death*. This result is most important because this period of time has always been considered the most difficult to manage. Many surgeons believe that the patient with an acute ruptured aneurysm must wait days or even weeks before an operation, but a great many die during this period. The effectiveness of the medical method in the acute emergency period, by supplying valuable time, may improve the results of operations performed later. When the acute phase is over, some of these cases, valuated carefully with regard to cross circulation and other factors, may then become elective surgical cases. It may be possible to treat many inoperable cases with hypotensive drugs alone indefinitely.

Fortunately, effective treatment in these cases does not require correction of the basic defect. Strictly speaking, the best the surgeon is able to do in clipping an aneurysm is to obliterate only the part of the aneurysm adjacent to the fundamental weakness in the vessel wall. In other words, neither medical nor surgical methods actually correct the underlying cause of illness.

Even after an apparently successful operation, the clips on an aneurysm sometimes slip off with subsequent refilling of the aneurysm and recurrent hemorrhage. Still another surgical difficulty has been reported in which cervical carotid ligation was performed for intracranial aneurysm but, after the carotid ligation, a cervical carotid aneurysm adjacent to the ligature occurred.[7] This raises the question of the incidence of iatrogenic aneurysm, which, though low, should be borne in mind.

Fig. 3. Angiogram showing aneurysm of anterior cerebral artery in patient 65 years old at time of hemorrhage and treatment. She recovered.

CONCLUSIONS

Experience with this method has been primarily with *emergency* cases of ruptured aneurysm, and the results are better than those of surgical methods. It is now suggested that the medical method be used in the acute stage of hemorrhage under the conditions described. Then, after the patient has survived the acute phase, decision as to subsequent management must depend upon comparison (in the future) of long-term results of the medical method with the results of other methods.

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Effect of induced localization on incidence and distribution of experimental allergic encephalomyelitis

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IN THE PRESENT STATE of knowledge, it seems possible that the mechanism involved in remissions in multiple sclerosis is related to that which operates to produce remissions in experimental allergic encephalomyelitis (EAE). Prigal[1] has suggested that remissions in EAE (and perhaps in multiple sclerosis) are due to combination of brain antigen with antibrain antibody. The work reported here is an attempt to determine whether damaged brain tissue can absorb enough of the noxious agent (antibody?) of EAE to influence the course of the experimental disease.

Clark and Bogdanove[2] showed that electrolytic lesions and other forms of brain damage induced localization of EAE in the adjacent tissue. Levine[3] showed localization of EAE in and around cyanide lesions. Both the electrolytic and cyanide lesions were permeable to trypan blue, suggesting that increased penetration of a noxious agent may have been responsible for localization. EAE in the normal rat affects the spinal cord more than the forebrain,[3,4] but some rats with induced forebrain localization around cyanide lesions of the corpus callosum, corpus striatum, and other areas had little or no EAE in their cords.[3] This observation raised the possibility that the cord had been protected because the presumed noxious agent of EAE had been diverted to and absorbed by the forebrain,[3] analogous to the diversion of noxious agent by parenteral injection of brain tissue ("substitute brain").[5] Such a mechanism, if confirmed, might provide evidence for the theory that spontaneous remissions in EAE are due to absorption of noxious agent in the EAE lesions. The present experiments were designed to elucidate the extent and mechanism of apparent "sparing" of spinal cord in rats with EAE and cyanide encephalopathy.

METHODS

The main experiments were performed on 72 female albino rats of a Wistar-derived strain. Half of this lot (weight, 185 to 245 gm.) were given 120 mg. of guinea-pig spinal cord in Freund's adjuvant, divided into 7 simultaneous intracutaneous injections of 0.1 cc. each (technic of Lipton and Freund[4]). Nine or ten days later, 24 of these rats, selected at random, were exposed to hydrogen cyanide. The exposure was repeated thirteen or fourteen days and again sixteen or seventeen days after the injections in order to produce severe, widespread lesions. The 12 rats not exposed to cyanide served as controls. All surviving rats, experimental and control, were killed with chloroform twenty days after the injections. Five weeks later, the entire experiment was repeated on the remaining 36 rats (weight, 219 to 370 gm.).

Cyanide exposures. Hydrogen cyanide was generated by bubbling air through 100 cc. of 5% potassium cyanide. The rats, each in a separate glass jar, were brought to a nearly lethal degree of intoxication (previously described as stage 3[6]) after five to ten minutes and were maintained in that state for twenty minutes. In previous experiments,[3,6] gas mixtures flowed continuously, but, in the present

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work, cyanide was delivered intermittently as needed to induce and maintain stage 3 intoxication and there was no gas flow during periods of optimum effect. This "static" technic resulted in a low mortality rate; it is more fully described elsewhere.[7]

Histopathologic methods. Brains were removed, fixed in buffered 10% formalin, cut in 2- to 3-mm. coronal slices, and embedded in entirety in paraffin. Spinal columns were divided into 5 segments, fixed, and decalcified, after which the spinal cords were removed and embedded longitudinally in entirety. Sections were stained by hematoxylin-eosin and, in some cases, by luxol fast blue–periodic acid–Schiff–hematoxylin. Slides were scored as positive for EAE if there was even a single typical vascular and perivascular lesion; doubtful or questionable lesions were recorded as negative. Severity was estimated in arbitrary grades of 1 to 4+. In view of the limitations of such an arbitrary and subjective grading, the spinal cords in each experiment were ranked according to severity of EAE by the method of paired comparisons.[8] The slides were coded, and all possible pairs were recorded on slips of paper for subsequent random selection. Each pair of slides was selected, examined, and compared, and entries of 1 for the member of the pair with more severe EAE and 0 for the member with less severe EAE were made in an appropriate table. The sum of all entries for each slide constituted a score which indicated the rank in order of severity. The coefficient of consistence[8] was unity, showing that no inconsistent observations had been made (that is, $A>B>C>A$).

In the second experiment, all hearts were sectioned in entirety but no significant lesions were found.

Anoxic-ischemic experiment. It was of interest to determine whether induced localization of EAE, previously demonstrated for electrolytic lesions[2] and cyanide lesions,[3] would occur with other types of brain damage. For this purpose, anoxic-ischemic lesions were produced by combining unilateral common carotid artery ligation with anoxic anoxia induced with nitrous oxide;[9] 24 rats (weight, 126 to 239 gm.), divided into 4 groups, were given guinea-pig spinal cord in Freund's adjuvant in doses of 120 mg. (divided among 7 sites), 17 mg. (single site), 1.7 mg. (single site), and 0.17 mg. (single site). Thirteen or fourteen days later, the right carotid arteries were occluded by "blind ligation,"[9] and this was followed by nitrous oxide which produced a state of unconsciousness for twenty minutes. Controls included 24 rats that received spinal cord in adjuvant divided into 4 dosage groups as above but were not subjected to the anoxic-ischemic procedure or were "blind ligated" without subsequent nitrous oxide. Another control group of 12 rats was given Freund's adjuvant mixed with saline (instead of spinal cord), followed by ligation plus nitrous oxide, or ligation alone, or neither. All surviving rats were killed eighteen to twenty-four days after initial injections (four to eleven days after anoxic-ischemic procedure). Slides were coded and read without knowledge of the group to which the animal belonged.

RESULTS

EAE produced hind-limb paralysis in some of the rats. Cyanide produced weakness, apathy, and circling movements in some severely damaged animals. Frequently, it was difficult to differentiate symptoms of EAE and cyanide encephalopathy, especially those appearing soon after exposure. Many rats had no symptoms despite positive histologic results for either or both conditions.

Cyanide lesions. The 48 experimental rats were exposed to hydrogen cyanide 3 times except for 5 animals whose poor condition after 1 or 2 exposures precluded further treatment. Only 11 rats died before termination of the experiments; these plus a single rat that survived but failed to have cyanide lesions were excluded from the study. The remaining 36 rats exhibited severe cyanide encephalopathy affecting multiple anatomic structures (Table 1). On the average, there were cyanide lesions in 3.6 different structures, whereas only 2.5 structures per rat were affected in the previous study (Table 1 of Reference 3). (The difference between these figures is significant at probability level $p=0.01$.) This increase was due largely to a much higher incidence of thalamic and cortical lesions and was attributed to altered technic, particularly employment of multiple exposures.

Induced localization of EAE. Of the 36 ex-

TABLE 1
DISTRIBUTION OF EAE AND CYANIDE LESIONS IN 36 EXPERIMENTAL RATS

Experiment 1				Experiment 2			
EAE lesions*			Location of cyanide lesions‡	EAE lesions*			Location of cyanide lesions‡
Forebrain†	Hindbrain	Cord		Forebrain†	Hindbrain	Cord	
Spinal cord and brain positive for EAE							
4	3	3	CSHCoTCe	4	1	3	CSHCoT
4	1	2	CSHCoT	3	0	2	CSHCoT
3	2	3	SCoT	3	0	1	SHT
3	3	1	SCo	2	3	4	SCoT
2	2	3	SHCoT	2	1	2	CST
2	0	1	CSHCoTR	1	0	2	CSHT
1	0	1	CHT	1	1	1	SCo
Brain positive but cord negative for EAE							
4	1	0	SHCoT	3	1	0	CSHT
4	0	0	CSHCoTN	3	0	0	CST
2	0	0	SHCoTCeR	2	0	0	CSHCoT
2	0	0	SCoT	2	0	0	CSHT
2	0	0	CSCo	2	0	0	HT
1	0	0	SHCoCe	1	0	0	CSHCoTN
1	0	0	SCoN	1	0	0	CST
				1	0	0	CHT
Both brain and cord negative for EAE							
0	0	0	CSHCoT	0	0	0	CST
0	0	0	CSH	0	0	0	CT
0	0	0	CH	0	0	0	HT
				0	0	0	H

*O = absent; 1 to 4 = grades of increasing severity
†Forebrain EAE localized in and around cyanide lesions
‡C = callosum; S = striatum; H = hippocampus; Co = cerebral cortex; T = thalamus; N = substantia nigra; Ce = cerebellum; R = callosal radiation

perimental rats with cyanide lesions, all but 7 had EAE as well (Table 1). In every instance, there was clear evidence of localization of EAE in and around cyanide lesions, confirming the previous report.[3] This interpretation was based on the typical morphology of the vascular and perivascular lesions of EAE. The combined lesions frequently showed augmented inflammatory reaction, with hypercellularity and even foci of malacia, but, in every instance, the diagnosis of EAE was supported by the presence of typical vascular lesions as well. Not infrequently, EAE was localized around 1 or 2 damaged structures but not around other areas that showed equally severe cyanide lesions.

There was no difficulty in differentiating the typical lesions of EAE from relatively slight endothelial swelling and adventitial proliferation that occur in uncomplicated cyanide encephalopathy; furthermore, the vascular reaction in uncomplicated cyanide lesions is limited to the confines of the damaged area in contrast to the characteristic satellite arrangement of EAE vessels in combined lesions. (This differentiation has been illustrated in a previous publication.[3])

Incidence of EAE. The occurrence of EAE in control and experimental series is detailed in Table 2, with the positive group subdivided according to involvement of forebrain, spinal cord, or both. The experimental series had an

81% incidence of EAE, while the control group had only 54%. The difference of 27% between these figures is more than twice the standard error of the difference and is therefore significant at probability level p=0.05.

Inspection of Table 2 reveals that the increased incidence of EAE in the experimental series was due to forebrain EAE, that is, to EAE localized in and around cyanide lesions. Every cyanide-treated rat that showed EAE had the disease in the forebrain, often exclusively in the forebrain with no involvement of cord. None of these rats had positive cord and negative forebrain. In contrast, control rats frequently had positive cord and negative forebrain, and none had negative cord and positive forebrain. The observation of increased incidence of EAE due to forebrain localization in the experimental series may be interpreted as due to lowered threshold for development of EAE in the presence of cyanide lesions. According to this interpretation, the difference between 81% positive in the cyanide-treated series and 54% positive in the control series represents a group of rats that would not have had EAE were it not for the presence of cyanide lesions.

The experimental rats show not only increased EAE in forebrain but also decreased incidence of EAE in spinal cord (Table 3). However, the difference between control and cyanide-treated series in this regard is relatively small, about the same magnitude as the standard error of the difference and therefore not significant at probability level p=0.05. When these results are subdivided between the 2 experiments (Table 3), the lack of agreement throws even more doubt on their significance. In addition, there was no difference in severity of spinal cord EAE in the 2 series when studied by the method of paired comparisons. Table 4 shows the arrangement in order of severity for the second experiment; there is no evidence of sparing of the cords in the experimental series compared to controls. In fact, the average ranks in experiment 2 were almost equal and, in experiment 1, showed slightly more severe lesions in the cyanide-treated series. Therefore, if the presence of cyanide lesions in the forebrain (with consequent localization of EAE therein) had any sparing effect on the cord, the effect was too small to be established by these experiments in terms of decreased incidence or decreased severity.

TABLE 2

COMPARISON OF EAE INCIDENCE IN CONTROL AND EXPERIMENTAL (CYANIDE-TREATED) RATS

	EAE		Number of rats	
	Forebrain	Spinal cord	24 controls	36 experimental
EAE positive	+	+	7 (29%)	14 (39%)
	+	—	0 (0%)	15 (42%)
	—	+	6 (25%)	0 (0%)
Total			13 (54%)	29 (81%)
EAE negative	—	—	11 (46%)	7 (19%)

TABLE 3

INCIDENCE OF EAE IN SPINAL CORDS OF CONTROL AND EXPERIMENTAL (CYANIDE-TREATED) RATS

	Control		Experimental	
Experiment 1	8/12	(67%)	7/17	(41%)
Experiment 2	5/12	(42%)	7/19	(37%)
Combined	13/24	(54%)	14/36	(39%)

TABLE 4

HISTOPATHOLOGIC RANKING OF EAE IN 12 SPINAL CORDS

Code*	Total score†	Severity‡	Source
Y	11	4	Experimental
O	10	4	Control
P	9	3	Control
N	8	3	Experimental
V	7	2	Control
Q	6	2	Experimental
S	5	2	Experimental
R	4	2	Experimental
W	3	1	Experimental
X	2	1	Experimental
T	1	1	Control
V	0	1	Control

*Coded slides arranged in order of rank (descending order of severity)

†Total scores obtained from all possible paired comparisons

‡Severity in grades of 1 to 4+

Anoxic-ischemic experiment. Of 24 experimental rats, 8 were lost due to early death after nitrous oxide exposure. Of 16 survivors, 12 had anoxic-ischemic lesions, 10 had EAE, and 8 had both conditions coexisting. The anoxic-ischemic lesions affected the right cerebral cortex, hippocampus, corpus striatum, thalamus, and midbrain, as described previously.[9] The EAE lesions in 7 of these 8 rats were clustered in and around the anoxic-ischemic lesions. A high degree of objectivity could be maintained in evaluation of induced localization because the anoxic-ischemic lesions were strictly unilateral and localization of EAE lesions could be seen upon simple comparison of right and left sides of the forebrain. A rat with induced localization had no evidence of EAE elsewhere in the brain or cord; similar instances have been noted above in connection with cyanide experiments. A rat with severe EAE in the cord and a few lesions on both sides of the forebrain showed no localization around anoxic-ischemic lesions. The control rats with EAE showed greater involvement of the cord and hindbrain than the forebrain, as did controls in cyanide experiments. Control rats given Freund's adjuvant without nervous tissue showed no EAE around anoxic-ischemic lesions or elsewhere.

DISCUSSION

The phenomenon of induced localization of EAE, previously demonstrated for electrolytic[2] and cyanide lesions,[3] has now been confirmed and extended to anoxic-ischemic lesions. In addition, we have shown that induced localization in and around cyanide lesions is associated with an increased incidence of EAE. This cannot be due to any nonspecific effect of histotoxic anoxia because the increased incidence was accounted for by a group of rats that had EAE located exclusively in and around their cyanide lesions. This specific effect of the cyanide lesions may be interpreted as evidence of a lowered threshold for EAE. It is possible that the presence of cyanide lesions merely accelerated the appearance of EAE in a group of rats that would have had it at a later date, had they been left undisturbed. Therefore, the term "lowered threshold" applies only to the situation at the time of sacrifice. The demonstration by Bogdanove and Clark[10] that local exacerbations of EAE can be induced in animals recovered from an attack of EAE by placing electrolytic lesions in their brains fits in with our evidence that the lesions lower the threshold for EAE.

Electrolytic, cyanide, and anoxic-ischemic lesions have been associated with impairment of blood-brain barrier manifested by trypan blue staining, leading to the assumption that increased penetration of a noxious agent was responsible for induced localization of EAE.[2,3] On the other hand, Bogdanove and Clark pointed out that trypan blue stained only the electrolytic lesion and not the surrounding tissue in which localization of EAE had been noted.[10] However, Brierley's studies[11] with labeled phosphate and diiodofluorescein have demonstrated increased radioactivity not only in areas of necrosis produced by cold injury and in surrounding edematous brain tissue but also in distant areas including the opposite hemisphere. It is of interest that Brierley attributed increased activity in remote areas to vasodilation, increased blood flow, and increased endothelial area rather than to altered permeability, but either mechanism allows for augmented passage of the noxious agent of EAE. It is possible, also, that activation of cells in vessel walls or uncovering of intracellular antigens in and near necrotic areas may play a role in induced localization of EAE.

Our main objective in this work was to determine whether induced localization of EAE in the forebrain would result in sparing of other regions of the nervous system, particularly the spinal cord, presumably by diversion of some noxious agent. Paterson[12] has already provided some experimental evidence for such a possibility. He found that the blood level of passively administered antibrain antibodies remained constant for two hours in normal animals but decreased rapidly in animals with brain lesions of a type associated with impaired blood-brain barrier. This suggested that the circulating antibodies had been absorbed in the damaged area. In our experiments, the rats had relatively mild EAE (which presumably means relatively little noxious agent) and severe, widespread cyanide lesions (to absorb the noxious agent). Nevertheless, we were unable to demonstrate a significant degree of sparing of the cord.

Several factors may have obscured a sparing effect on the spinal cord. The forebrain cyanide lesions may have been induced too late because EAE may develop in a small number of rapidly reacting rats before the tenth day.[13,14] On the other hand, the cyanide lesions may have already lost part of their increased permeability by the time EAE developed in some of the slowly reacting rats;[11,15] induced localization of EAE around brain lesions decreases as the lesions age.[3] The breakdown of blood-brain barrier, although maximal around the forebrain lesions, may have affected the spinal cord to a small extent, perhaps during the short periods of cyanide exposure.[16] The volume of damaged brain tissue may not have been sufficiently large to absorb all the noxious agent; other workers have injected nervous tissue in large quantities in attempts to suppress EAE by diversion of noxious agent to the "substitute brain,"[5,17] and supression of EAE by injection of brain extract was proportional to dosage.[18]

We conclude, therefore, that, if induced localization of EAE in and around forebrain cyanide lesions actually resulted in absorption of a noxious agent, the diversion was not of sufficient magnitude to result in significant sparing of the spinal cord but that a number of factors may have interfered with demonstration of a sparing effect. In other words, the supply of noxious agent proved inexhaustible under the conditions of these experiments. These observations do not disprove the theory that spontaneous remissions in EAE are due to absorption of noxious agent within areas of damage, but neither do they lend support to this hypothesis.

SUMMARY

Severe cyanide encephalopathy was produced in rats by 3 consecutive hydrogen cyanide exposures during the incubation period of experimental allergic encephalomyelitis (EAE). Incidence of EAE in rats with cyanide lesions was greater than that in controls. The increased incidence was attributed to lowered threshold for EAE in and around areas damaged by cyanide. Despite extensive localization of EAE in and around cyanide lesions in the forebrain, it was not possible to demonstrate a significant degree of protection against EAE in the spinal cord. If the presumed noxious agent of EAE was absorbed in the forebrain lesions, the diversion was not of sufficient magnitude to spare the spinal cord.

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A preliminary report on the measurement of Parkinson's disease

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In 1956, the Department of Veterans' Affairs, Ottawa, allocated a research grant to Dr. Elliott for the investigation of pallidectomy as a treatment for Parkinson's disease. At the outset of this project, it was realized that an objective system for measurement of the patient's salient disabilities would have to be developed. It was clear that clinical impressions obtained from standard methods of examination could not provide a reliable index of the patient's progress. The results of neurologic examination can rarely be stated in quantitative terms; moreover, when two examinations of the patient are made several months apart, it is almost impossible to assess small changes in, say, the rigidity of limb musculature. The initial goal, therefore, was to develop a set of tests for routine use which would provide an objective assessment of the patient's condition. The requirements for these tests were that they should [1] measure functions closely related to the patient's disabilities, [2] provide numerical measurements of the patient's functions, and [3] be rapid and simple to operate and not require the presence of personnel with specialized training.

Our intention is to develop ultimately a battery of tests to which each patient who is a candidate for pallidectomy will be exposed both before and after operation. These tests will eventually provide information about the control of skeletal muscle of the limbs, respiratory movements, autonomic control of bladder, and the like. However, the choice of tests that fulfill the requirements listed above cannot proceed rapidly, and we have begun with the design and trial of a series of tests to measure the control of skeletal muscle in the limbs.

The tests we are currently using for limb function can be conveniently divided into two categories—those which are most sensitive to rigidity of muscles and those which are most sensitive to tremor.

TESTS FOR RIGIDITY OF LIMB MUSCLE

We have found that the maximum speed of movement at joints provides a simple and sensitive measure of rigidity. Thus, while a normal individual can readily flex and extend the forefinger some 115 times in thirty seconds, many parkinsonian patients with rigidity cannot exceed a frequency of 50 per thirty seconds.

Finger movement. In order to measure mobility of a finger, the patient is asked to press and release with his finger the key of a commercial digital counter (of the type used for counting blood cells) as often as possible during a thirty-second period. The patient's score is then read from the numerals of the counter at the end of the trial. This test can be applied to any finger, but our observations have been restricted to the performance of the forefingers of each hand, as mobility of this finger is important to the efficiency of most hand functions.

Wrist movement. For tests of mobility, the patient's arm is placed palm down upon a heavy wooden board with the wrist lying between 2 wooden pegs so adjusted that only abduction and adduction movements of the wrist are possible. He is then requested, using 1 finger, to press alternately and as rapidly as possible the keys of 2 mechanical counters separated by a distance of 5 in. His score is then read at the end of the test period of thirty-seconds. Figure 1 shows a photograph of the wooden board upon which are mounted 3

From the Parkinson's Project, Queen Mary Veterans' Hospital, Montreal.

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counters; any single counter may be used for tests of finger movement, while the right-hand pair are used for testing lateral movement of the wrists.

Elbow movement. In order to test elbow movement, the center counter and the 2 wooden pegs are withdrawn from the board. The subject is then asked to rest his elbow upon the board. He is instructed to use 1 finger to depress the keys of the 2 remaining counters alternately and as rapidly as possible for a thirty-second period. These 2 counters are separated by a distance of 12 in.

Tests of mobility of joints in leg. The tests used for movement of the ankle, knee, and hip joints are essentially similar to the tests described above for movement of the joints of the forearm; 2 electrical foot-pedal switches were screwed to a heavy wooden board. These switches were placed 12 in. apart, and depression of either switch was used to operate an electromechanical counter. Mobility of the ankle is assessed by requesting the patient to depress and release 1 of these switches as frequently as possible, using 1 foot with the heel resting upon the board. When the patient is seated, mobility of the knee joint can be tested by asking him to depress alternately the 2 foot switches set 12 in. apart so that flexion and extension of the leg at the knee are required to reach them.

With the patient sitting and the knee flexed, the same 2 switches set 12 in. apart determine the speed of abductor-adductor mobility of the hip joint. This can be done forwards and backwards for flexors and extensors of the hip with the patient standing.

TESTS FOR TREMOR OF LIMB MUSCLE

Electromyogram. Undoubtedly the most sensitive estimate of parkinsonian tremor is provided by the electromyogram. While the patient is lying at rest on a bed, simultaneous electromyograms of all 4 limbs are recorded; 2 standard type electroencephalograph electrodes are fastened with collodion to the dorsal aspect of each forearm 15 cm. apart and another 2 to the lateral surface of each leg 20 cm. apart. The use of 2 electrodes upon each limb ensures that the record provides a measure of activity in muscles lying beneath and between the electrodes. The 4 simultaneous

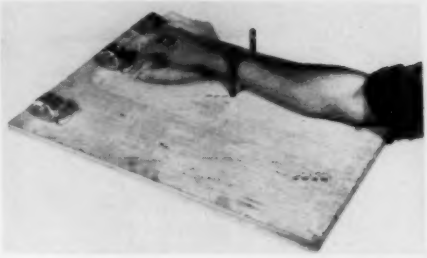

Fig. 1. Wooden board with counters used for tests of finger and wrist movements

electromyograms are recorded by ink-writing pens on paper, with a time constant of one-eighth second and a gain of 50 μv. per centimeter. In analyzing the records made in this way, both the dominant frequency of the electromyogram and the mean peak-to-peak amplitude in microvolts during an approximate fifteen-minute period were recorded.

Mechanical tremor tests. The tests described below are applicable to forearm tremor only. The patient is asked to rest only his elbow upon the table and hold a metal stylus so that it lies between 2 converging metal bars without touching either. Figure 2 shows a photograph of the instrument, which was obtained from the Lafayette Instrument Company of Indiana. Every time the electrified metal stylus held by the patient touches one of the guide bars, an electromechanical counter is operated, a buzzer sounds, and a light flashes on. Thus, the number of his errors during a thirty-second trial is scored automatically. It will be seen that the 2 metal guide bars converge, making

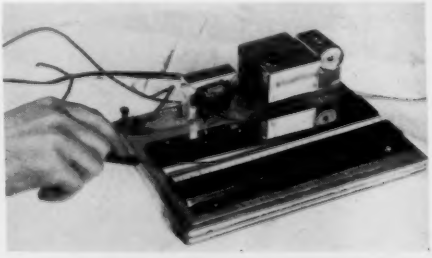

Fig. 2. Instrument for forearm tremor tests

it possible to adjust the difficulty of the task to the patient's abilities. Patients presenting tremor before operation were in fact always asked to hold the stylus at a point at which they regularly scored more than one error in three seconds. The same target point is used in all subsequent tests.

Fig. 3. Apparatus to test finger dexterity

TESTS FOR FINGER DEXTERITY

Figure 3 shows a photograph of the apparatus used for tests of finger dexterity; this was also obtained from the Lafayette Instrument Company. Using the hand to be tested, the patient is asked to pick up the small metal pins one at a time and place them in any of the available holes; score is recorded as the number of holes so filled in thirty seconds.

PRESENTATION OF RESULTS

The scores obtained from the tests described above can be used in a number of different ways. Thus, where a measure of the severity of parkinsonian symptoms is required, one can

TABLE 1

DATA OBTAINED FROM PATIENT A. L. BEFORE AND AFTER RIGHT PALLIDECTOMY*

Test	*Side tested*	February 3	February 17	March 3		March 10	March 17	September 22	Average control
						A. Movements in thirty seconds†			
Forefingers	Left	32	66	54	PALLIDECTOMY	107	99	78	108 ±8.1
	Right	79	140	135		126	134	113	121 ±6.3
Wrists	Left	23	27	23		22.5	27	24	35.7±0.9
	Right	35.5	39.5	39		31	38.5	31.5	40.7±1.4
Elbows	Left	21.5	22.5	21.5		17.5	20.5	18.5	23.8±1.1
	Right	35	34.5	31.5		23.5	32.5	25.5	28.1±2.0
Pins	Left	6	7	7		8	5	9	14.5±1.0
	Right	14	13	15		14	13	14	13.7±1.3
Mechanical tremor, arm	Left	119	25	130		0	0	0	0
Electromyogram, arm (mean peak-to-peak μ.v.)	Left	78	——	——		<5	——	——	<5
						B. % normality of movements on left side‡			
Forefinger		30	61	50	RIGHT	99	92	72	100
Wrist		64	76	64		63	76	67	100
Elbow		90	94	90		73	86	78	100
Pins		41	48	48		55	35	62	100
		C. u/o index§				*C. u/o index§*			
Forefinger		0.40	0.47	0.40		0.85	0.74	0.67	
Wrist		0.63	0.68	0.59		0.72	0.70	0.76	
Elbow		0.61	0.65	0.68		0.74	0.63	0.72	
Pins		0.43	0.54	0.47		0.57	0.39	0.64	

*Patient and controls were all right handed.

†Section A gives actual figures recorded. Average control figures were obtained from 6 healthy persons of ages 50 to 62, 4 men and 2 women. Average control performance is given together with standard error of mean.

‡Figures are percentages derived by dividing patient's performance by that of average normal control.

§Figures were obtained by dividing values of unoperated side by those recorded from operated side.

express the maximum number of movements per second that a patient is capable of performing at a particular joint as a percentage of the average performance with the same joint of a control series of healthy subjects of similar age. Such estimates of the per cent normality for the test scores of one patient are provided in Table 1. It will be seen that this measure of the incapacity fluctuates considerably from day to day; the fluctuation is of course the consequennce of the well-known instability of parkinsonian signs.

We have been less interested in developing tests to assess the severity of parkinsonism than in designing some measurements to provide a reliable index of the benefits of pallidectomy. Since the operation is usually unilateral, it is possible to use the limbs on one side of the body as a control for changes induced in the limbs contralateral to the side of operation. Thus, in the case of a right pallidectomy, we have used as an index of left forefinger mobility the scores obtained for the right forefinger divided by the scores obtained for the left forefinger; this fraction will be referred to below as the "unoperated-operated" (u/o) index. Table 1 provides the original scores obtained from patient A. L. for various arm movements. These results have been selected because the crude scores obtained from the 3 examinations of the patient made before operation show considerable fluctuation. It will be seen that these fluctuations are necessarily reflected in estimates of the per cent normality, or percentage of control values, as shown in section B of Table 1. However, when the preoperative values obtained from the side being studied are compared with the opposite side by presenting them as the u/o index, as shown in section C of Table 1, it will be seen that the index (for this or any other patient) becomes relatively constant. This relative constancy comes about because the factors responsible for the fluctuations seen from time to time

TABLE 2
U/O INDEXES OF 3 PATIENTS RECEIVING PALLIDECTOMY

		Time of testing in weeks			*Mean u/o index before operation*	*Side of operation*			
Patient		1	2	3			4	5	31
A. L.	Forefinger	0.40	0.47	0.40	0.42		0.85	0.74	0.69
	Wrist	0.65	0.68	0.59	0.64		0.72	0.70	0.76
	Elbow	0.61	0.65	0.68	0.65	Right	0.74	0.63	0.72
	Pins	0.43	0.54	0.47	0.48		0.57	0.39	0.64
	Electromyogram, (Left arm) (mean peak-to-peak μv.)	78	———	———	———		<5	———	———
G. C.	Forefinger	1.04	1.06	1.04	1.05		1.04	———	———
	Wrist	0.76	0.93	0.84	0.84		0.83	———	———
	Elbow	0.88	1.00	0.96	0.95	Left	0.82	———	———
	Pins	0.75	0.86	0.80	0.80		1.07	———	———
	Electromyogram, (Right arm) (mean peak-to-peak μv.)	———	13.4	———	———		1.6	———	———
L. S.	Forefinger	0.31	0.64	———	0.48		0.67	———	———
	Wrist	0.36	0.51	———	0.43		0.50	———	———
	Elbow	0.51	0.80	———	0.66	Right	0.50	———	———
	Pins	0.81	0.60	———	0.70		0.70	———	———
	Electromyogram, (Left arm) (mean peak-to-peak μv.)	———	———	———	———		———	———	———

affect both sides equally, and so both numerator and denominator of the u/o index change together.

Table 2 is presented in order to illustrate the results that can be obtained with the tests described above. Patient G. C. was selected as an example of a patient presenting with tremor and little rigidity. Patient A. L. displayed both rigidity and tremor. The conditions of patients G. C. and A. L. were considerably improved by pallidectomy. Patient L. S. has been chosen as an example of a subject who apparently received no benefit from pallidectomy.

The following paragraphs provide brief clinical descriptions of the 3 patients in Table 2.

Case 1. Mr. A. L., aged 58, first noticed mild tremor of the left arm after a blast injury of the body and head in 1917, but it has been much worse since 1937. When first seen in 1959, he had tremor of the head and the whole left side of the body, particularly the arm. Definite weakness in the left arm and leg and slight weakness of the right ankle were noted. The tremor in the left arm was most marked in the fingers, and the left-sided rigidity affected movements at the shoulder, elbow, and wrist. Some adductor rigidity of the left thigh was found, which gave him a slightly rolling gait.

The operation performed was a right-sided pallidectomy using a wire-loop leukotome. The tremor of the left foot stopped before the leukotome was withdrawn, and, within three minutes, the tremor disappeared in the left hand. The patient also found the left hand easier to use, an improvement which has been sustained for ten months. The electromyogram after the operation showed no tremor, whereas it had been clearly recorded from the left arm and leg before operation. At the time of writing, the patient was returning to work.

Case 2. Mrs. G. C., aged 65, had tremor of the right arm and, to a lesser extent, of the right leg for three years. Disability was mainly social; she felt self-conscious about holding cards while playing bridge and about clumsiness when eating. Nevertheless, she was able to perform all the functions of daily living for herself and did her own housework, though she employed help and her husband helped her as well, to reduce fatigue. Her tremor was mainly of the right fingers, wrist, and forearm, with true muscular weakness in these same parts. There was less tremor in the left hand and wrist, together with some weakness. Rigidity with cog-wheeling was felt in the neck muscles, both forearms, and right leg, and there was slight bilateral tremor of the eyelids. Medically, there were no contraindications to operation, and she was not relieved by drugs, so a left-sided pallidectomy by means of a wire-loop leukotome was done. The patient was drowsy and sleepy for a few hours after the procedure but awoke the next morning with all her tremor gone on the right side. She had good strength in the right arm, hand, and leg and was very pleased with the result. The postoperative electromyogram showed no tremor in the right arm and leg in contrast to the preoperative record, in which there was marked and continuous tremor from both the right arm and leg.

Case 3. Mrs. L. S., aged 57, was a widowed schoolteacher who had tremor and weakness of the left arm for three years; These gradually became subdued by increasing rigidity of this limb as well as the other three, though the defects remained worse down the left side. She showed some excessive salivation, dyspnea, dysphagia worse for liquids than for solids, a tendency to greasiness of the skin, and falling while walking, particularly on icy surfaces. During one fall, she injured her left shoulder and now doesn't go out in such weather. She also had trouble turning in bed, had to have her meat cut, and required help taking a bath. Otherwise, she was ambulant and able to perform most of the functions of daily living. The voice was weak and monotonous, and the mouth could only be partly opened. The neck was stiff in all movements, and she was unable to place the chin on the chest or to extend the neck. Bilateral adductor rigidity of the thighs and rigidity at the hips, knees, and ankles on both sides were noted. This resulted in a form of scissors gait. The rigidity in the arms was present at all joint levels; abduction of the left shoulder, which had been injured, was limited to 45 degrees. The hand grips were surprisingly strong. Tremor was only elicited by asking the patient to strain at some action such as putting on her own coat, which brought out tremor in the left forearm. The electromyogram showed very little tremor. Otherwise, medically, she was in good health, and, because drugs failed to relieve her, a right-sided pallidectomy by means of a wire-loop leukotome was performed.

After the operation, the patient remarked that she no longer had the sensation of difficulty in swallowing liquids, which was hard for her to describe, and it was obvious that her speech was a little stronger. She was more cheerful and felt less stiff on the left side, but there was no clinically evident reduction of tremor and the adductor rigidity of the thighs and the scissors gait were still present. The result of the operation was considered poor.

DISCUSSION

Preliminary stages in the design of a battery of simple tests for measurement of the symptoms of parkinsonism have been described. We are certainly not the first to attempt such tests. Schwab and Prichard[1] have devised a similar series of tests for the purpose of assessing therapy in Parkinson's disease. They measured:

- The strength of hand grips with a dynamometer
- The number of index finger to thumb proximations in ten seconds
- The time to draw 10 circles 6 cm. in diameter
- The time to get up from a chair and stand
- The time to walk a measured ten-meter course.

Rigidity, tremor, and freedom of arm swinging were assessed clinically and graded on a scale from 0 to 4+. Brennan[2] also describes a clinical method of assessing tonus and voluntary movement which is semiobjective in the sense that presenting signs are graded into 4 or 5 categories.

An electromyographic study of voluntary movement in paralysis agitans was made by Blake Pritchard[3] thirty years ago using a string galvanometer. Since then, there have been many electrical studies of tremor in parkinsonism. Hoefer and Putnam[4] made an extensive study of the electromyogram in tremor and rigidity as recorded with both surface and intramuscular electrodes. Bishop, Clark, and Price[5] made an extensive study of the surface electromyograms of tremor voluntarily induced by normal individuals and that occurring spontaneously in parkinsonian cases. Schwab and Prichard[1] also assessed tremor from electromyographic tracings made with surface electrodes. Muscle tone has been studied by Agate, Doshay, and Curtis[6] and by Spiegel and associates.[7] Webster[8,9] has developed an elaborate and very accurate method for the simultaneous recording of the strength, tremor, and rigidity of forearm muscles. Boshes and associates[10] have designed an apparatus using strain gauges for quantitation of tone, tremor, and speech.

It is easy to find signs of Parkinson's disease which are simply measured, and the choice of measurements for any battery of tests will largely depend upon local facilities. Nevertheless, in our opinion, satisfactory tests must [1] be simple and rapid to operate; [2] measure functions closely related to the patient's disabilities; [3] provide numerical measurements of the patient's functions which correspond roughly with clinical assessment; and [4] provide some information about all parts of the peripheral motor system—the skeletal muscle of limbs, muscles of respiration, muscles controlled by the autonomic nervous system, and so forth.

The few tests described above have only been concerned with malfunction of the limb muscles but were selected as a pilot study with the intention of applying similar tests to other regions of the body. They appear in practice to fulfill most of our requirements.

Perhaps it should be stressed that the tests we have described are in no way diagnostic. They were never intended to differentiate a cerebellar tremor from the parkinsonian type, nor could they separate rigidity from spasticity or any other form of akinesia. They were intended as numerical measures of the severity of signs in cases in which the clinical diagnosis was already established. From this point of view, the pilot tests described above have proved successful. They have provided estimates of incapacity which corresponded well with clinical assessment of the day-to-day variation in the patient's condition; moreover, they appear to enable one to describe the results of treatment in numerical terms.

The tests of movements at joints (those in which the subject was asked to flex and extend particular joints as rapidly as possible) appear to measure mainly rigidity and are little affected by parkinsonian tremor. Patient G. C. presented clinically, as we have said, with a severe bilateral tremor but only slight rigidity, which persisted after operation. Her forefinger movements were estimated as about 80% normal. It will be seen from Table 2 that pallidectomy produced a dramatic reduction in the patient's tremor with no significant change in the movement scores. Patient A. L., on the other hand, presented with both severe rigidity and severe tremor. His forefinger movements were estimated as approximately 45% normal on the affected side. Pallidectomy produced an immediate improvement in both rigidity and tremor with corresponding improvements in both movement and electromyographic scores (Table 2).

The ideal measure of tremor is undoubtedly the electromyogram made with intramuscular electrodes, which we are planning to use in the future, having used surface electrodes initially. On the other hand, this method of recording with relatively complex apparatus

and the subsequent analysis of records are extremely time-consuming. We are at present constructing a unit to record the electromyogram on magnetic tape, which will allow us to analyze such parameters of tremor as frequency and amplitude with electronic computing apparatus available at McGill University. Nevertheless, in the absence of electronic apparatus, a simple mechanical tremor tester such as the one described above seems satisfactory. However, the instrument used in this study proved to have a disadvantage. Some patients would rest the metal stylus against one or the other of the metal guides and thus score only one error when, in fact, their tremor was severe. The present instrument is therefore being altered so that the target for the stylus has no raised borders and tremor can drive the stylus tip in any direction without obstruction. Moreover, we intend to modify the instrument so that it records the percentage of time "off target."

As might be expected, the "pin test" for manual dexterity is sensitive to both tremor and rigidity. An almost identical test has been used by Kaplan, Machover, and Rabiner.[11]

The small number of cases examined in these preliminary tests does not permit more than guesses at the generalities of Parkinson's disease. Nevertheless, we have the impression that movements of the fingers are usually more severely crippled by rigidity than are movements of the wrist and elbow joints. Moreover, when pallidectomy is successful, the recovery of finger mobility is far more dramatic than is that of wrist or elbow movement. The generalization is well illustrated by the results obtained from the patient A. L., which are listed in Table 1; it will be seen that, while there is a dramatic improvement in finger movement after operation, there is really no change in either the elbow or wrist mobility. It does not follow that the particular sensitivity of finger movement to rigidity indicates a specific effect of the disease upon the motor neurons of finger musculature. We presume, on the other hand, that, because rigidity restricts speed of voluntary movement, the normally rapid movements of fingers are more sensitive to the disease than are slower movements at the larger joints. We would conclude from these observations that measurements of the mobilities of the index fingers provide the most sensitive measure of rigidity of musculature in the arm.

We intend, in the near future, to extend our battery of tests so as to provide a broader quantitative assessment of the signs of parkinsonism. The purpose of these measurements is to provide an objective basis for estimating the results of pallidectomy, and it is hoped that a preliminary report can be made in the near future on the results of this operation in a small number of cases.

SUMMARY

1. Some simple, objective, quantitative tests for rigidity and tremor in Parkinson's disease are described.

2. These tests were not designed to be diagnostic but to provide quantitative measurements of the patient's disabilities, which have corresponded well with the impression gained from clinical examination.

3. The tests have been used to assess the results of surgical treatment.

The authors would like to express their thanks to Dr. Donald Lloyd-Smith for providing the electromyography facilities and reports and to Dr. Harold Elliott for his continual encouragement and advice.

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Electroencephalographic observations in a case of meprobamate poisoning

Capt. Sanford Meyerowitz, M.C., U.S.A.R., and
Capt. Richard Satran, M.C., U.S.A.R.

SEVERAL WORKERS have reported the effect of meprobamate upon the electroencephalogram. A review of the literature, however, reveals no reports of serial electroencephalographic observations during acute meprobamate poisoning or of the duration of the electroencephalographic effects induced by such an overdose. The following is a brief report concerning a patient who ingested 8 gm. of meprobamate shortly after a base-line electroencephalogram was obtained; serial electroencephalograms were then recorded.

CASE REPORT

In January 1959, a 19-year-old unmarried Caucasian soldier came to the Mental Hygiene Clinic complaining of fainting spells, chest pain, shortness of breath, and acute episodes of anxiety. The examination revealed a slender, listless-appearing young man who was extremely passive and anxious. He weighed 140 lb. General physical and neurologic examinations showed no abnormalities. An electroencephalogram was obtained to rule out the existence of a cerebral dysrhythmia (Fig. 1). In subsequent visits to the Clinic, further data were obtained regarding his background, personal and family medical history, and his marked dissatisfaction with military life. The diagnostic impression was that of personality disorder with symptoms of anxiety, as well as several hysterical conversion symptoms, one of which was syncope. He was given a week's supply of meprobamate tablets with the instruction to take 1 tablet three times a day. Three days later, he ingested 20 tablets (8 gm.) all at once in what was interpreted as a suicide gesture.

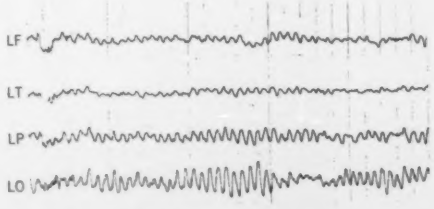

Fig. 1. "Control" electroencephalogram

The patient was brought to the hospital emergency room approximately four hours after taking the drug. His systolic blood pressure ranged from 80 to 96 mm. Hg; the diastolic was 60 mm. Hg. Respirations were 20 to 22 per minute. At that time, he was very difficult to arouse. He would respond to insistent, loud verbal stimuli but barely to painful tactile stimuli. His speech was slurred. The pupils were 4 to 5 mm. in diameter and reacted minimally to light. His control of oral secretions was unimpaired. Generalized flaccidity of all muscle groups was noted, and the deep tendon reflexes were markedly depressed. No pathologic reflexes were found.

The patient's hypotension was treated conservatively. Urinary output was recorded and considered adequate. Twenty-four hours after admission, he was alert and responded well to all stimuli except pinprick. Some nystagmus was noted on lateral gaze. Tests of coordination were carried out, and the finger-to-nose test was done with much past pointing. The heel-to-knee-to-toe test was done well but slowly. Deep tendon reflexes were more easily elicited and also more active in the legs than in the arms. The patient's speech was still

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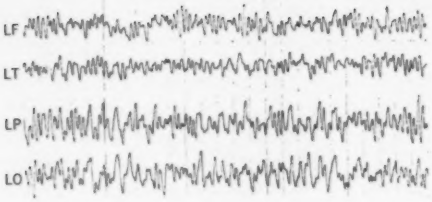

Fig. 2. Record made twenty-eight hours after ingestion of meprobamate

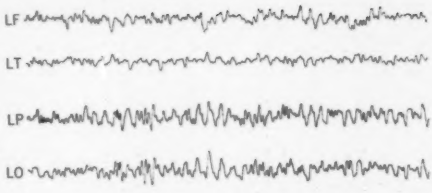

Fig. 3. Electroencephalogram made forty-four hours after ingestion of drug

slightly slurred. Routine urinalysis and hemogram were normal. Forty-eight hours after admission, the patient's condition was much improved and he was walking and speaking without difficulty.

ELECTROENCEPHALOGRAPHIC FINDINGS

Electroencephalograms were recorded one, two, four, and fourteen days after the drug was taken. An 8-channel Grass Machine, Model No. 111D, was used. The base-line electroencephalogram (Fig. 1) made eleven days before drug ingestion reveals a well developed synchronous record of moderate voltage with 10-per-second alpha activity and no abnormalities.

The record made twenty-eight hours after the drug (Fig. 2) is characterized by high voltage, rhythmic, fast activity, preponderant in the anterior leads, with frequency ranging from 17 to 22 per second and with amplitude from 30 to 140 μv. Some high voltage, 5- to 6-per-second waves are seen predominantly in the posterior leads.

Forty-four hours after the drug, the record (Fig. 3) shows a basic frequency of 19 to 23 per second in the anterior leads, less synchronous than in the preceding record, with amplitude now reduced to 25 to 35 μv. The somewhat random moderate to high voltage slower activity in the posterior leads is more prominent.

At ninty-one hours after the drug (Fig. 4), there is a general return to rhythmic synchronous 8-to-10 per second activity; amplitude is still 25 to 35 μv. No fast activity persists. Some 5- to 7-per-second moderate to high voltage waves still appear in brief runs. The record is now similar to the base-line recording except for the presence of this slower activity.

The record obtained fourteen days after drug ingestion is not shown. It is identical with the base-line record except for a single brief synchronous run of 6- to 7-per-second high voltage waves in the parietal leads.

DISCUSSION

Several workers have described low voltage fast activity in the electroencephalogram with meprobamate. There is agreement in the description of such activity in several studies of patients maintained on usual or moderately high doses of the drug for varying periods of time.[1–3]

Mengoli and Maccagnani,[4] however, describe no significant modifications of the electroencephalogram in a group of patients taking meprobamate in doses as high as 8 gm. per day. Similarly, no electroencephalographic changes could be observed by Glotfelty and Wilson[5] in a group of patients taking therapeutic amounts of the drug for a relatively brief period.

Effects of a single, moderately large dose have been reported. Pfeiffer and associates[6] report that, in the human subject, meproba-

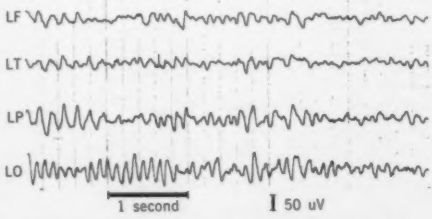

Fig. 4. Record made ninety-one hours after ingestion of drug

mate in single oral doses of 1.6 to 2 gm. produces 20- to 30-per-second low voltage activity not unlike the fast activity seen with the barbiturates and paraldehyde. Henry and Obrist[2] obtained similar results after single oral doses of 2 to 3.2 gm. in human subjects.

Numerous clinical reports of cases of meprobamate overdosage have been made. A few of these include some electroencephalographic observations,[7,8] but in none was the patient studied with serial records.

In the case reported here, after a large acute dose, high voltage fast activity is seen for longer than twenty-four hours. Similar activity was noted by Henry and Obrist[2] in some of their patients receiving smaller doses. Miletto, Collomb, and Cardaire[9] also reported a tendency toward increased amplitude. However, increased amplitude with the drug has not been generally observed. In the case presented here, at forty-eight hours the amplitude is reduced but fast activity persists. This now resembles the low voltage fast activity reported by the majority of workers cited here, whether studying the acute or chronic effects of the drug.

Also observed here is some slower 6- to 7-per-second activity persisting for as long as fourteen days after the drug; this slow activity is not seen in the base-line record. The significance of this finding in a single case is elusive.

SUMMARY

A case of meprobamate toxicity with serial electroencephalographic observations is reported. The findings are in general agreement with other reports of the effect of smaller doses of the drug on the electroencephalogram.

The authors wish to acknowledge the technical help of Specialist William T. McKissock, AMEDS, U. S. Army.

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Announcing

Chartered Air Transportation for Members of the American Academy of Neurology

The Officers and the Board of Trustees of the American Academy of Neurology have given their approval to a proposal that the members of the Academy be solicited concerning their desire to form a group which will charter air transportation to and from the various neurological congresses which are to be held in Europe in 1961.

The American Academy of Neurology under no circumstances can assume responsibility for such arrangements but it has authorized the Treasurer, Dr. Charles M. Poser, to conduct such solicitation and make the necessary arrangements with a travel agency. This offer will apply only to members of the American Academy of Neurology and their immediate families.

The cost of a charter flight is determined by dividing the cost of the aircraft by the number of people in the plane. This includes children over the age of two who, therefore, must pay full fare. Children under the age of two go free. In order to obtain the lowest rate, all seats should be full. In the event that the response is such that total plane loads are incomplete, assignments will go to those who reserve first. The requests will be taken in order according to the postmark date.

It is proposed that air transportation be chartered between New York and Paris, Paris being most centrally located since the meetings will be held in Munich (neuropathology) and Rome (neurology, neuroradiology, EEG, genetics, etc.).

Alternate suggestions, including departure from the West Coast over the polar route will be entertained.

Since many members will want to combine this with vacations, it is suggested that the group depart from New York on or about September 1, 1961, and return from Paris on or about September 30, 1961.

Use of DC-7 equipment will result in the cost of approximately $280.00 per person round trip, while jet equipment will raise it to approximately $350.00 per person round trip. The cost is naturally determined by the number of people, as explained above, the aircraft being rented as a unit.

Our final contract with the airline must be signed two months before actual departure date. It will, therefore, be necessary that the full price be paid in advance. Many airlines also require that a 10% deposit be paid at the time that the actual equipment and date of departure have been decided upon. Every participant in this project must sign up for a round trip.

A down payment of $50.00 per person will have to accompany the signed request for reservations. This deposit will naturally be refunded should the number of participants be insufficient to arrange for at least one charter plane load to and from the meetings. This deposit will also be applied to the 10% deposit required and the full payment.

Members of the Academy who are interested are requested to fill out the attached questionnaire which is to be considered to be a request for a reservation and return it with their deposit fee as soon as possible prior to January 1, 1961.

Please fill in form below and return to:

CHARLES M. POSER, M.D., Treasurer, A.A.N.
University of Kansas Medical Center, Kansas City 12, Kansas

REQUEST FOR RESERVATION OF CHARTERED AIR TRANSPORTATION TO CONGRESSES – SEPTEMBER 1961

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Are you listed in the 1959 edition of the A.A.N. Directory? Yes _____ No _____

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- Please indicate if you prefer destination to be: PARIS LONDON ROME
- Please indicate if you would prefer return to be from: PARIS LONDON ROME
- Please indicate if you would prefer to leave from the West Coast via the polar route.
- It is suggested that departure date be on or about September 1 and return on or about September 30, 1961. Please indicate if you would prefer

a different departure date: _____

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I agree to pay full round-trip price for all reservations (exact amounts will depend upon the equipment and the number of passengers per plane load) at least 2 months before actual departure date or at the time requested.

Ten per cent of the total fare may be requested as a deposit a few weeks after equipment and departure date have been decided. The enclosed deposit will be applied to the full payment.

Signature: _____

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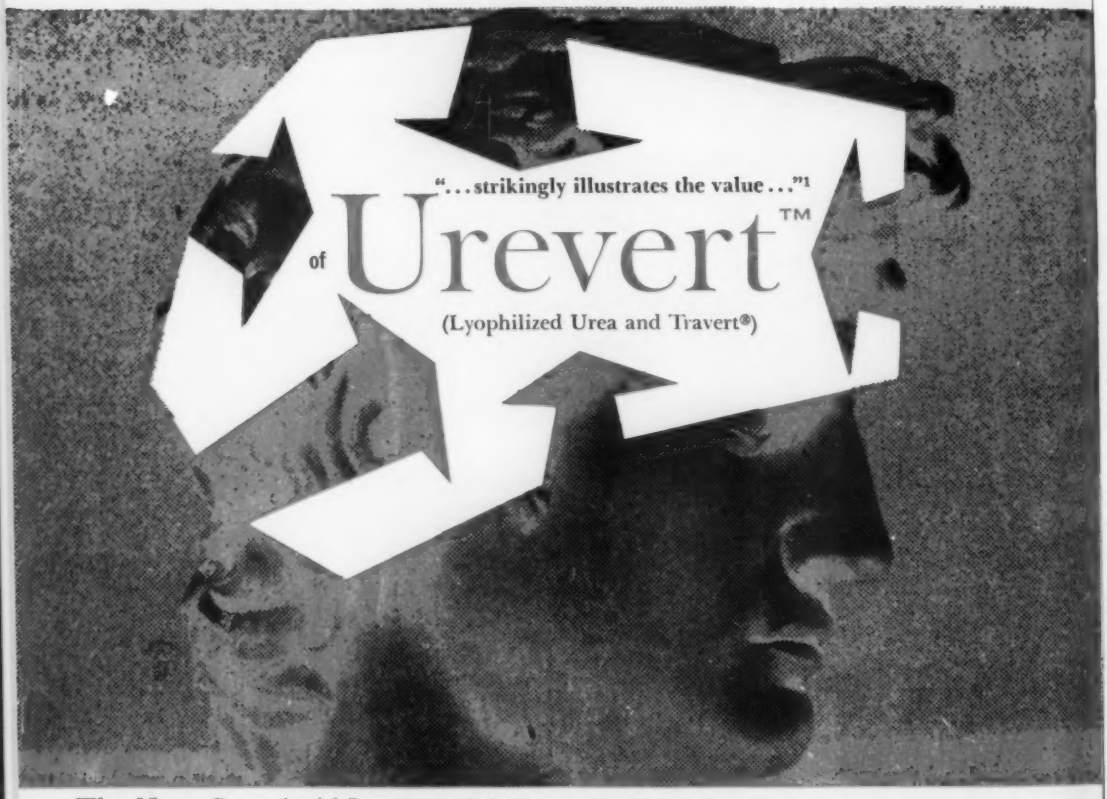

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1. Taheri, Z. E.: Urevert in Cranial Trauma and Brain Surgery, J. Internatl. College of Surgeons 32:389 (Oct.) 1959.
2. Javid, M.: Urea—New Use of an Old Agent, Reduction of Intracranial and Intraocular Pressure, The Surgical Clinics of North America, Philadelphia, W. B. Saunders Company, Aug. 1958, p. 907.

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NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

DECEMBER 1960

Augustus S. Rose, M.D., President
A. L. Sahs, M.D., President-Elect
Joseph M. Foley, M.D., Vice-President
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Scientific Sessions of 1961 AAN Meeting The scientific sessions of the Thirteenth Annual Meeting of the American Academy of Neurology will be conducted at the Sheraton-Cadillac Hotel in Detroit April 27 through 29, 1961. The deadline for abstracts of papers-from-platform has passed (December 1, 1960). The deadline for abstracts of scientific exhibits and demonstrations, not exceeding 150 words, is December 30, 1960. These should be mailed to Richard D. Walter, M.D., University of California Medical Center, Los Angeles 24. If motion pictures are to be used, any unusual projection requirements should be indicated. Joseph M. Foley, Seton Hall College of Medicine, Jersey City 4, N. J., is Chairman and Coordinator of the Scientific Program Committee....Further information on the 1961 AAN program will be forthcoming in subsequent issues of the Newsletter.

Neurologic-Neurosurgical Meetings Under the auspices of the Centro de Estudos Egas Moniz and the Gulbenkian Fund and the World Federation of Neurology, a two-day symposium on the "Organization of the Nervous System" was conducted in the Students' Hall of the Hospital Escolar de Santa Maria in Lisbon October 21 and 22. The program had been organized by Georges Schaltenbrand (Wurtzburg) and Almeida Lima (Lisbon). There were 2 morning sessions (9 A.M. to noon) of formal reports, each followed by an afternoon session (4 to 8 P.M.) devoted to discussions of the reports. Local arrangements were directed by Almeida Lima assisted by Miller-Guerra. Among the rapporteurs were A. Hopf (Neustadt); Clinton N. Woolsey (Madison); F. Bremer (Brussels); E. Bay (Düsseldorf); H. Hécaen (Paris); and A. E. Walker (Baltimore). In addition, there was a distinguished group of discussors including Paul C. Bucy (Chicago), Edouard Busch (Copenhagen), Klaus Conrád (Hamburg), Richard Jung (Freiburg), and Almeida Lima (Lisbon). Sessions were conducted in English, French, and German. Plans are in progress for the publication of the reports and résumé of the discussion by Professor Schaltenbrand....The day preceeding the Lisbon symposium (October 20), a group of delegates from the World Federation of Neurology and the Executive Committee of the World Federation of Neurosurgical Societies assembled in Lisbon to develop a program of improved liaison and collaboration between neurologists and neurosurgeons throughout the world. The

delegates representing the Executive Committee of the World Federation of Neurosurgical Societies were Paul C. Bucy (Chicago), E. H. Botterell (Toronto), and Bronson S. Ray (New York). After preliminary deliberations, the delegates of both Federations voted unanimously to establish a joint liaison committee of 12 with a chairman and secretary, subject to modification by the Executive Committees of both Federations. They further voted that the present group serve as a provisional committee for the formulation of preliminary plans until the meeting of the Executive Committees of both Federations, about one year hence. Mogens Fog of Copenhagen and Bronson Ray of New York (Secretary-General of the Second International Congress of Neurological Surgery, Washington, D.C., October 14 through 20, 1961) were nominated chairman and secretary, respectively, of the provisional committee.

California To Feature Conference on Paraplegia

John D. French, President, announces that the Los Angeles Society of Neurology and Psychiatry, in collaboration with the California Spinal Cord Research Foundation, will conduct a conference on "Recent Contributions of Basic Research to Paraplegia" in Los Angeles February 17 and 18, 1961. The conference will highlight contributions by leading basic science investigators of North America in such areas as "Regeneration in the Central Nervous System," "Pain Mechanisms and Problems," "Spinal Reflex Mechanisms," and the "Pharmacology and Biochemistry of Paraplegia." The basic science authors will then join eminent clinicians in a round-table discussion on "Present and Future Implications of Basic Science Contributions to Clinical Paraplegia." Also included in the program is a visit to the Paraplegia Center of the Veterans Administration Hospital, Long Beach, Calif....Invitations to attend the conference will be furnished upon request within seating capacity limits. Programs and further information may be obtained from Robert P. Sedgwick, M.D., Secretary-Treasurer, Los Angeles Society of Neurology and Psychiatry, 2010 Wilshire Boulevard, Los Angeles 57.

UCP's Advisory Committees Meet in Boston

United Cerebral Palsy's Clinical and Research Advisory Committees held their respective fall meetings in the Jimmy Fund Building of Boston November 4 through 6, 1960. On November 5, the 2 committees combined for an informal scientific session, chaired by Samuel P. Hicks, to hear reports by investigators in the Boston area who are supported by United Cerebral Palsy's Research and Educational Foundation. In addition to the reports given by UCP's grantees, a progress report on the status of NINDB's collaborative perinatal program was presented by Duncan Reid. Both UCP committees were housed at the Statler-Hilton Hotel.

ANA 1960 Transactions Now in Press Melvin D. Yahr, Secretary of the American Neurological Association, announces that the 1960 edition of the Transactions of the American Neurological Association, now in press, will be published and distributed by the Springer Publishing Company, 44 East 23rd Street, New York 10. Previously, the Transactions were published by The William Byrd Press, Inc., Richmond, Va....The ANA's 1961 Annual Meeting will be held in the Claridge Hotel, Atlantic City, June 12 through 14, 1961.

AAN Establishes Position and Personnel Registry Maynard M. Cohen, AAN Committee on Membership and Placement, announces that the American Academy of Neurology has established a registry of available positions and personnel in neurology and the neurologic sciences. Purpose of the Registry is twofold: first, to aid academic institutions and physicians in private or group practice in filling available positions with individuals properly trained in these fields, and, second, to make known the availability of appropriate positions to clinical neurologists and neurologic scientists who are about to complete their training or who wish to relocate....For this purpose, the Registry maintains lists of both positions available and candidates seeking such positions and their qualifications. The ultimate goal is to place interested parties in direct contact with one another....To place listings in the Registry, it is necessary to complete and return an appropriate application form, which may be procured by writing to the AAN Executive Offices, 4307 East 50th Street, Minneapolis 17, Minn. If requested, information in the Registry is kept confidential.

Here and There The American Board of Psychiatry and Neurology announces that its 1961 examinations will be held in New Orleans, March 20 and 21 and in Chicago October 9 and 10.... The annual meeting of the American Epilepsy Society (American Branch, International League Against Epilepsy) meets in the Sert Room of New York's Waldorf Astoria Hotel on December 8, 1960, the day before the meetings of the Association for Research in Nervous and Mental Disease. The morning program of the Epilepsy Society will be devoted to a symposium on "Changing Concepts of Focal Epilepsy."...Gilbert H. Glaser, Secretary, announces that the annual meeting of the Medical Board of the Myasthenia Gravis Foundation will be held at the Hotel Roosevelt in New York City on Friday evening, December 9, 1960....An official delegation of 6 British neurologists, under the direction of Hugh Garland (Leeds), were guests of the Academy of Science of the Romanian Peoples' Republic September 10 through 20. Academician Kreindler (Bucharest) had arranged for the British visitors a general scientific program, visits to hospitals and institutions, and sight-seeing excursions.

Briefs Peter Kellaway is resigning as Director of the Blue Bird Children's Clinic for Neurological Disorders in Houston, Texas, in order to devote more time to research. Acting on his recommendation, the trustees will appoint a pediatric neurologist as director and make this a full-time appointment. Announcement of the new appointment is expected shortly....At the Ninth Reunion of the German Society of Electroencephalography in Düsseldorf. Heinz Caspers of the Institute of Physiology at the University of Münster was awarded the Hans Berger Prize....Carlos Chagas, Director of the Institute of Biophysics of the University of Rio de Janeiro, was awarded the Moinho Santista Prize September 15, 1960, for his contributions, using scientific materials native to Brazil, to biophysics. This prize (often called by Brazilians the Nobel Prize of Brazil) is awarded every five years and carries with it a cash award of 1 million cruzeiros, tax-free.

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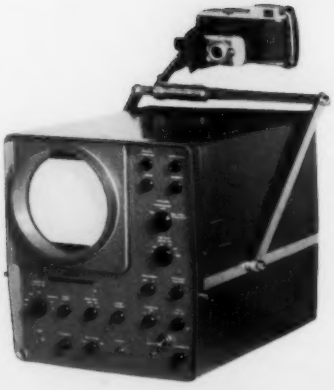

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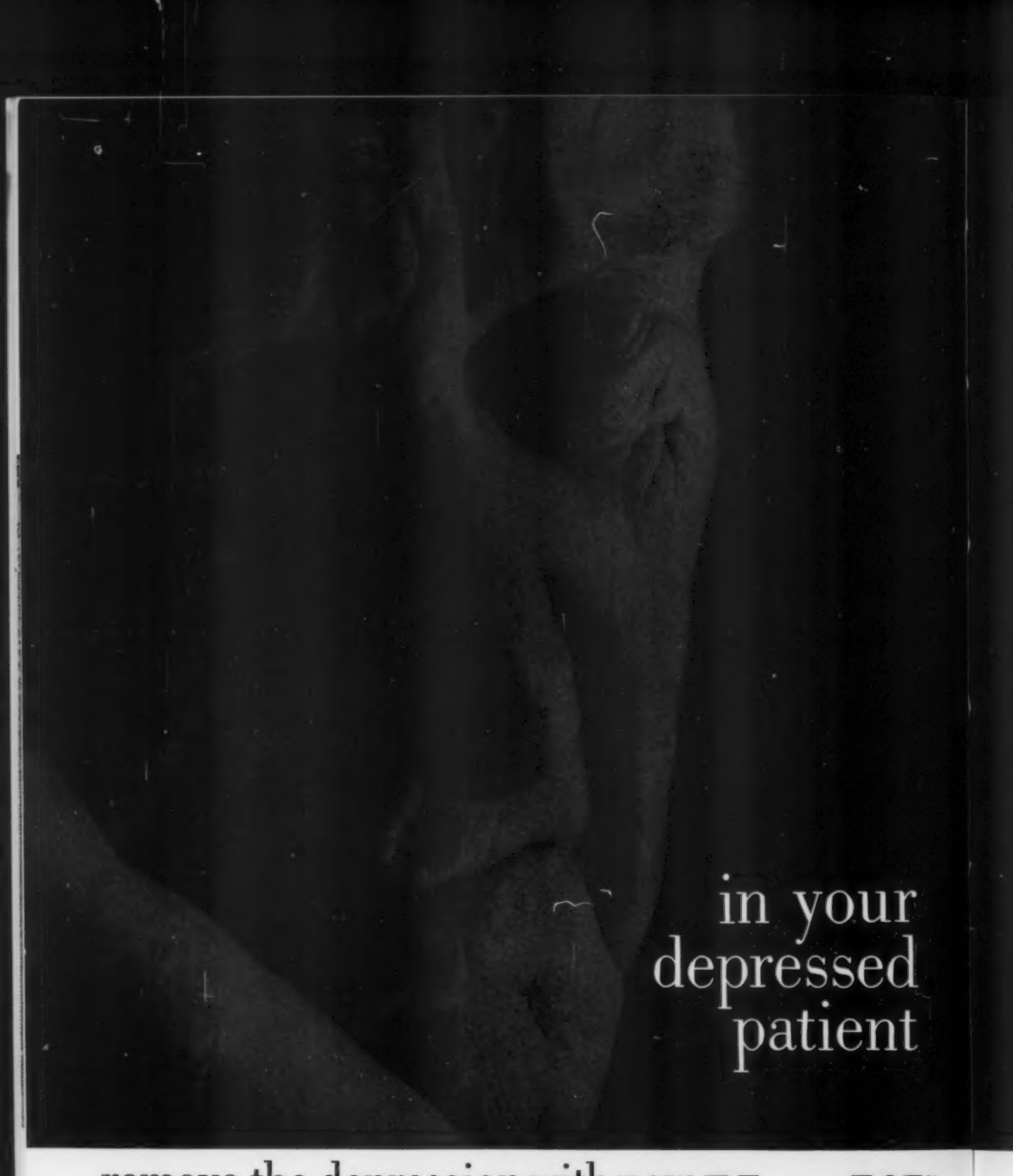

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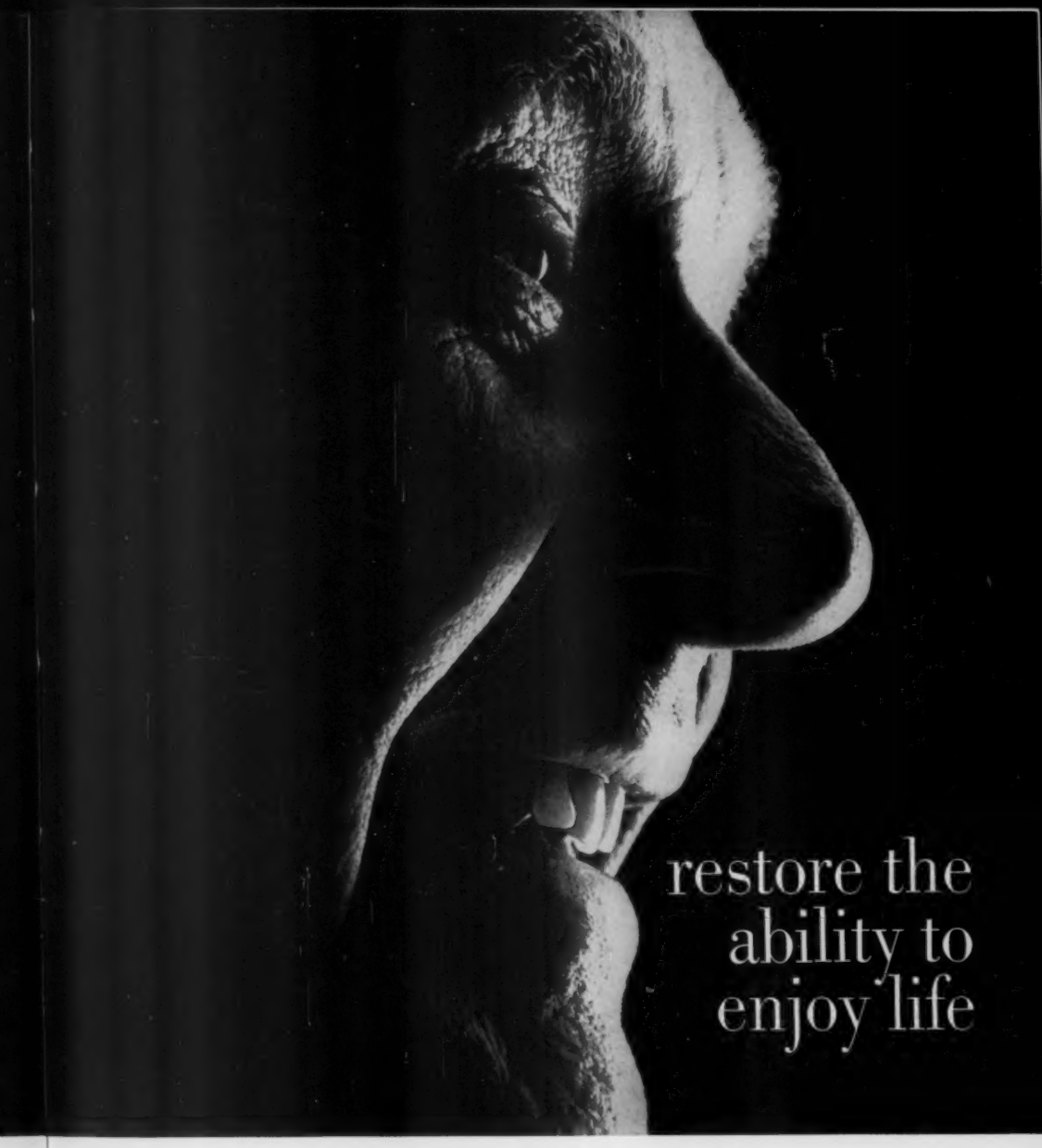

INDICATIONS: Mild to severe depressions, depressions associated with chronic diseases such as angina pectoris and rheumatoid arthritis. Improves the depressed phase of affective (manic-depressive) psychosis, and relieves the depression of catatonic schizophrenics, although not affecting the psychosis *per se*. SIDE EFFECTS: Occasional postural hypotension and infrequent nausea, ankle edema, delayed micturition or constipation are managed by appropriate adjunctive therapy, or dosage reduction. DOSAGE: One tablet three times a day. After remission, reduce to a maintenance level of 1 or 2 tablets a day. SUPPLIED: Orange-coated tablets, each containing 15 mg. of phenylethylhydrazine present as the dihydrogen sulfate. Bottles of 100. CAUTION: Nardil should be withheld or used with extreme caution where the patient has a history of liver disease or liver damage is present. Hypotensive patients should be under close medical supervision.

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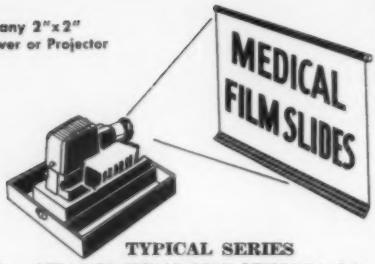

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